CASE REPORT

Orbital apex syndrome secondary to granulomatosis with polyangiitis

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SUMMARY

Orbital apex syndrome (OAS) is an optic nerve dysfunction with palsy of the third, fourth and sixth cranial nerves and ophthalmic division of the fifth cranial nerve. Causes can be infective, inflammatory, traumatic, neoplastic or vasculitic. We describe the first case in British literature and second worldwide of OAS presenting as granulomatosis with polyangiitis (GPA). A 38-year-old patient presented with left periorbital swelling and pain. An examination revealed left eye proptosis, tenderness in the ophthalmic distribution of the trigeminal nerve, unilateral ophthalmoplegia and reduced visual acuity. Initial treatment included intravenous antibiotics, steroids and nasal decongestants. Imaging demonstrated sinusitis and a suspected abscess from the infratemporal fossa to the orbital apex. However, sinus surgery showed granulation tissue without pus. The biopsy result was highly suggestive of GPA. A subsequent vasculitic screen was cytoplasmic-antineutrophil cytoplasmic antibody positive. This case highlights an unusual presentation of OAS secondary to GPA, as initial features suggested an infective cause.

BACKGROUND

Orbital apex syndrome (OAS) is a syndrome characterised by dysfunction of the oculomotor nerve (cranial nerve III), trochlear nerve (cranial nerve IV), abducens nerve (cranial nerve VI) and ophthalmic division (V1) of the trigeminal nerve along with optic nerve damage.¹ Cavernous sinus syndrome is distinguished from OAS by the additional involvement of the maxillary division (V2) of the trigeminal nerve. Superior orbital fissure syndrome has the features of OAS without optic nerve dysfunction.¹

The pathophysiology of OAS can be inflammatory, infectious, neoplastic, vascular, traumatic or iatrogenic in origin. Inflammatory disease causing OAS presents initially as painful ophthalmoplegia. It can be due to a spectrum of conditions including granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis.¹

GPA initially presents with head and neck involvement in up to 95% of the cases and the diagnosis is often made by an ear-nose-throat specialist.² A review of the literature has revealed that 60% of patients with GPA had ophthalmic manifestations. The spectrum of ophthalmic GPA includes conjunctivitis, scleritis, episcleritis, uveitis and retinitis.³

The pathophysiology of orbital inflammation in GPA is either from a primary granulomatous vasculitis or spread from the paranasal sinuses.⁴

This case highlights an unusual presentation of OAS secondary to GPA with no initial associated pulmonary or renal involvement. It demonstrates a diagnostic challenge as at presentation the clinical and radiological features suggested an infective cause.

CASE PRESENTATION

A 38-year-old woman presented with left periorbital swelling and pain, blurring of vision and absence of left eye movement 3 weeks following a dental extraction of the upper right fourth tooth and upper left second tooth.

Clinical examination revealed left eye proptosis and ptosis, with an upper lid margin to skin crease distance of 2 mm on the right and 6 mm on the left. Her visual acuity (Snellen chart) was 6/6 in the right eye 6/12–1 in the left eye, with no compromise in her colour vision (Ishihara chart assessment). Bilateral conjunctiva, cornea and fundi showed no abnormality. Intraocular pressures were normal bilaterally. She had left periorbital swelling and tenderness in the ophthalmic distribution of the trigeminal nerve accompanied by complete left eye ophthalmoplegia (cranial nerve III, IV and VI palsy; figures 1 and 2).

INVESTIGATIONS

Initial blood tests revealed slightly elevated inflammatory markers: white cell count at $13.3 \times 10^9/L$, C reactive protein at 19 mg/L and erythrocyte sedimentation ratio of 41 mm/h.

An orthopantomogram radiograph did not reveal any periapical lesion or dental abscess. A subsequent CT scan of the orbits and sinuses was requested.

The CT revealed diffuse left maxillary antrum opacification with some bony erosions of the medial wall. The medial wall of the left orbit also had bony erosions with protrusion of material into the extraconal space. Abnormality was noted in the left infratemporal fossa adjacent to the lateral wall of the left maxillary antrum involving masseter and

Figure 1 Initial presentation with left-sided periorbital swelling, proptosis and complete ophthalmoplegia.

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Figure 2 Outcome of improved proptosis and horizontal and vertical gaze following treatment.

pterygoid muscles and extending through the inferior orbital fissure into the orbital apex. The appearances were thought to be consistent with acute sinusitis with osteomyelitis and an abscess extending into the left orbit and infratemporal fossa (figures 3 and 4).

Following the scan a decision was made to proceed for urgent surgery with the intention of abscess drainage and sinus washout. She was also started on intravenous antibiotics and steroids.

During endoscopic sinus surgery no obvious infection was identified. There was a large amount of granulation tissue within the maxillary sinus and no pus. The lamina papyracea

Figure 3 Axial CT shows proptosis of the left orbit and shows encapsulated inflammatory soft tissue changes in the left orbital apex.

Figure 4 Coronal CT revealing opacification and thickening of antral walls of the left maxillary sinus.

was removed to decompress the orbit and biopsies of the granulations were sent for histological analysis.

The histology showed fibrous stroma incorporating a moderate-to-heavy infiltration of chronic inflammatory cells with foci of necrosis and eosinophil and neutrophil activity (figures 5 and 6). These appearances were suggestive of GPA. Special stains for fungi and acid fast bacilli were negative.

She had a tuberculosis interferon γ release assay (Elispot) which was negative. However, an antineutrophil cytoplasmic antibody (ANCA) screen was positive for cytoplasmic-ANCA (c-ANCA). Further, imaging included a CT scan of the thorax and MRI of the head. The CT scan of the thorax provided no evidence of pulmonary GPA. MRI showed left maxillary sinus soft tissue thickening involving the left pterygopalatine fossa and extraconal aspect of the left orbit. Mild abnormal signal was seen in the left infratemporal fossa involving the medial and lateral pterygoid muscles. These changes suggested inflammatory or neoplastic processes.

DIFFERENTIAL DIAGNOSIS

In this case infection, including tuberculosis, was the leading differential diagnosis with regard to causes of OAS, on account of recent dental extraction and CT findings.

Diagnosing the underlying cause of OAS is of vast importance as the management each of these conditions varies greatly and

Figure 5 Collection of histiocytes and multinucleated giant cells forming an ill-defined granuloma in proximity to a fibrosed blood vessel.

Figure 6 Elastic Van Gieson staining reveals a blood vessel with possible destruction of the wall and loss of staining.

without the correct treatment the patient's visual prognosis may decline.

TREATMENT

Initial treatment was for the suspected infection and abscess with antibiotics, steroid and decongestants, followed by surgical drainage.

Postoperatively, she continued on the steroids and antibiotics for 5 days while awaiting the histology results. Once the diagnosis of GPA was made she had urgent rheumatology input and started on intravenous cyclophosphamide treatment.

OUTCOME AND FOLLOW-UP

Once the patient had undergone orbital decompression and treatment with intravenous steroids, she had improvement to visual acuity (6/9 in the left eye) as well as vertical gaze within a week. She was subsequently managed as an outpatient by the rheumatology team.

DISCUSSION

Unique case and background of GPA

This is the first case reported in the British literature of OAS being the initial presentation of GPA. The only other case is reported in the French literature in a 10-year-old child.⁵ There have been cases reported of OAS in patients with an already established diagnosis of GPA.^{6–8}

GPA is a systemic inflammatory disease of unknown aetiology which can affect any organ. The classical or complete form of GPA affects the upper respiratory tract, lungs and kidneys. It can also occur in the limited form, which usually involves the head and neck, without any renal involvement and has a better prognosis.^{8–10}

Approximately 95% of patients with GPA first present with head and neck symptoms.^{2–9} Ophthalmic involvement is common and up to 60% of cases have been reported in a literature review from 1966 to 2005 by Pakrou *et al.*³

The most common ocular manifestations of GPA are kerato-scleritis and retroorbital mass lesions. However, the spectrum of ophthalmic involvement also includes mild conjunctivitis, scleritis, episcleritis, granulomatous sclerouveitis, retinal vasculitis, ciliary vessel vasculitis, nasolacrimal obstruction and dacryocystitis.³

Cranial nerve palsies and orbital inflammation occur in GPA by the spread of contiguous granulomatous lesions to the nerves through the paranasal sinuses or from arterial ischaemia due to the primary granulomatous vasculitic process.^{8–11} Visual symptoms in orbital GPA are from compressive or ischaemic optic neuropathy. However, proptosis remains the most common feature.⁸

Diagnostic challenges and CT findings

This case presented various diagnostic challenges. The initial differential diagnosis from clinic and radiological findings was of an orbital cellulitis and abscess secondary to sinusitis. The recent dental extraction and abscess was also a contributing factor to leaning towards an infective cause of OAS. There have been reported cases of OAS secondary to mucormycosis following a dental extraction.¹²

The CT findings were suggestive of an infective process, which is a more common cause for OAS.

The most common finding on CT imaging in GPA is of mucosal thickening, predominantly of the maxillary sinuses. Additional CT features include bony destruction, sclerosing osteitis and bony thickening of the nasal cavity, maxillary sinuses and mastoid cells.^{9–13}

The bony destruction is a result of a vascular necrosis due to obliteration of arteries by chronic inflammatory cell infiltrate and granulomas. Chronic granulomatous and vasculitic processes also cause chronic periostitis leading to new bone deposition and thickening.^{13–14}

In terms of imaging in GPA, CT scans may depict sinus involvement and orbital masses but an MRI is superior in illustrating granulomas and the extent of mucosal inflammation and ulceration in the sinuses, nasal cavity and orbits.¹⁰

Importance of c-ANCA and biopsies

ANCA are sensitive markers indicating an active form of GPA, particularly c-ANCA. The sensitivity of c-ANCA is 91% and the specificity is 99%. Approximately 80–90% of patients with GPA are positive for ANCA, with 80% of the cohort being c-ANCA positive.^{10–15} Levels of c-ANCA can indicate disease activity with normal levels demonstrating remission and better prognosis.^{8–16}

Tissue diagnosis is also necessary for the diagnosis of GPA. However, biopsies may be non-diagnostic, with up to 50% of cases requiring repeat biopsy. The site of biopsy is a major variable in diagnostic studies, with the best results from paranasal sinus tissue.⁹ The classical histological triad of GPA featuring vasculitis, tissue necrosis and granulomatous inflammation is only present in 50% of biopsy samples and therefore clinical correlation is of importance.^{10–17–18} This case reiterates the importance of histological analysis in diagnosing the cause of OAS.

Treatment and prognosis

The treatment of GPA should be prompt and aggressive once the diagnosis has been established from the consolidation of clinical, biochemical, histological and radiological features. Medical management comprises of remission induction therapy followed by maintenance therapy. This involves a lengthy course of systemic corticosteroids and immunosuppressive agents such as cyclophosphamide, methotrexate or azathioprin.^{3–15}

Cyclophosphamide acts by impairing DNA replication and transcription. In combination with glucocorticoids, it forms the gold standard induction therapy, achieving remission most

patients. However, it is associated with dose-dependent toxicity and morbidity.^{3 9}

Methotrexate is an alternative agent that acts as an antimetabolite. It is often used as a remission maintenance agent, but shows similar remission induction to cyclophosphamide in limited form GPA. Azathioprine is an alternative remission maintenance agent which acts by hindering DNA synthesis as a purine synthesis inhibitor.^{3 9}

Several other remission induction and maintenance agents are being investigated such as rituximab (chimeric monoclonal antibody), infliximab (tumour necrosis factor antagonist) and leflunomide (T-cell inhibitor).^{9 15}

Medical therapy forms the mainstay of treatment and can improve morbidity associated with ophthalmic and head and neck manifestations of GPA. However, in cases of severe orbital inflammation with proptosis, there is room for surgical interventions such as orbital decompression.³

The prognosis depends on the form, the stage at which treatment was started and the response to the treatment. Remission is often achieved within a year of treatment and survival rates are 95% at 5-year follow-up and 80% at 10-year follow-up.^{11 15 16} The 1-year mortality rate of untreated GPA is over 80% with a median survival of 5 months.³

Patients with multisystem GPA should be managed using a multidisciplinary approach by rheumatologists, ophthalmologist and otorhinolaryngologists.¹⁰

Learning points

- This case highlights an unusual presentation of orbital apex syndrome secondary to granulomatosis with polyangiitis (GPA) and demonstrates a diagnostic challenge.
- It also reiterates the significance of combining the clinical, biochemical, histological and radiological features in achieving a diagnosis of GPA, particularly the importance of obtaining biopsies.

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