



## Case report

## Successful reconstruction of an ocular defect resulting from granulomatosis with polyangiitis, following treatment with rituximab



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## ABSTRACT

**Purpose:** To report a unique case of orbital inflammatory disease which was ultimately diagnosed as granulomatosis with polyangiitis (GPA) and thus successfully treated.

**Observation:** A 47 year-old man presented with a rapidly progressive necrotic soft tissue mass within the medial antero-superior aspect of the right eyelid and orbit. He also had transient retinal vasculitis in the left. Serology, histology and imaging were atypical of, but consistent with, GPA. He was thus successfully treated with intravenous rituximab followed by reconstruction of the medial eyelid.

**Conclusion and importance:** A high index of suspicion of GPA is required in orbital inflammatory disease, especially when typical diagnostic findings are absent.

### 1. Introduction

Granulomatosis with polyangiitis (GPA) is a systemic vasculitis which typically affects the renal and respiratory systems, demonstrates ANCA positivity in 80–90% of cases. It is typically characterised histologically by granulomatous inflammation, necrosis and vasculitis.<sup>1</sup> There is ocular involvement in approximately 50% of cases, but this is most often part of multisystem disease.<sup>2</sup> We report here a patient who presented with severe, focal, necrotic, orbital inflammatory disease and who represented a diagnostic and therapeutic challenge. Despite an atypical presentation, based on a working diagnosis of GPA, he was successfully treated with intravenous rituximab followed by eyelid reconstruction.

### 2. Case report

A 48 year old Caucasian male presented with a lesion at the medial portion of the right upper eyelid. Present for two months, it had arisen initially as a small white pustular lesion which progressively enlarged and became erythematous before discharging purulent material. Topical fusidic acid and subsequently chloramphenicol ointments had no effect on the lesion. It increased dramatically in size following an attempt at incision and curettage at another hospital.

This man was otherwise well and denied symptoms of fatigue, fever, night sweats, weight loss, arthralgia, haemoptysis, rash, or haematuria.

He had had a cholecystectomy and the family history was unremarkable. His career and hobbies provided no unusual exposures to fungi or other infections.

On examination, the right eyelid was erythematous and edematous with a palpable mass in the superomedial aspect of the right orbit. Snellen visual acuity was 6/9 in the right eye and 6/6 in the left. The movements of his right eye were limited on attempted elevation.

C-reactive protein (CRP) was 36 mg/L (normal < 7) and erythrocyte sedimentation rate (ESR) 25 mm/hr (normal 0–20). No other immunological or biochemical abnormalities were noted. In particular, serum IgG4, rheumatoid factor, perinuclear and cytoplasmic anti-neutrophil cytoplasmic antibody (p- and c-ANCA), anti-nuclear antibody (ANA), extractable nuclear antigens (ENA), and Quantiferon gamma were all negative. Complement levels, thyroid function tests and angiotensin converting enzyme were normal. No micro-organisms were visualized at microscopy of, or cultured from, a sample of the discharge from the lesion.

Magnetic resonance imaging (MRI) orbits revealed a soft tissue enhancing mass within the medial anterosuperior aspect of the right orbit with resultant mild deformity and downward displacement of the right globe (Fig. 1).

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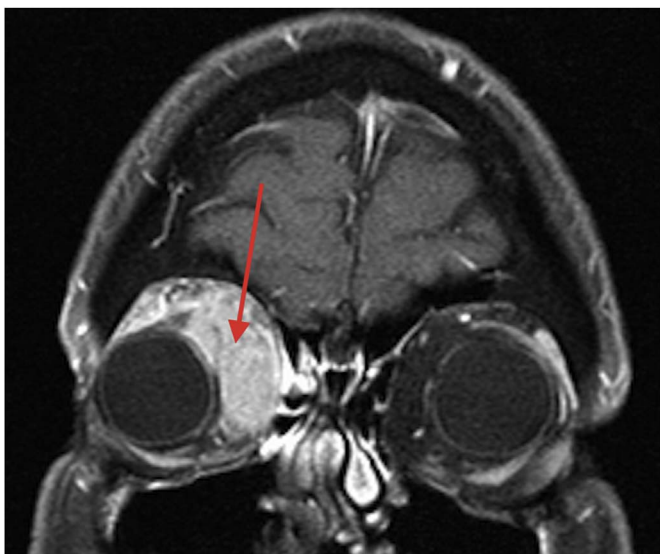


Fig. 1. Enhancing right periorbital mass on magnetic resonance imaging.

Considered in the differential diagnosis were infection (including atypical mycobacterial and fungal infection), orbital inflammatory disease (including GPA and immunoglobulin G<sub>4</sub> – related disease), sarcoid, lymphoma and other orbital malignancies including metastatic disease to the orbit.

CT thorax, abdomen and pelvis demonstrated no evidence of systemic disease.

The patient was empirically prescribed intravenous co-amoxiclav 1.2 g and metronidazole 500mg, both three times daily.

Biopsy of the lesion was performed via an upper eyelid skin crease incision. The tissues of the eyelid were found to be friable and the mass necrotic (Fig. 2A). Samples were sent for histological examination, microscopy and culture for bacteria, viruses and mycobacterium tuberculosis.

Histopathological analysis of the sample obtained demonstrated the presence sclerotic connective tissue and fat with very dense diffuse mixed inflammatory infiltrates of neutrophils, small and medium sized lymphocytes, macrophages, and plasma cells with neutrophilic micro-abscesses. The ratio of IgG4 vs. IgG positive plasma cells was 30%, with a maximum of 45 IgG4+ cells/high power field. There was no geographical necrosis, clear signs of vasculitis or well-formed granulomata. Immunohistochemistry revealed a mixed population of lymphocytes which marked primarily as T lymphocytes, and molecular analysis revealed polyclonal arrangements. This picture was deemed to be in keeping with a reactive inflammatory process. No micro-organisms were visualized at microscopy or cultured from the sample obtained at biopsy (Fig. 3).

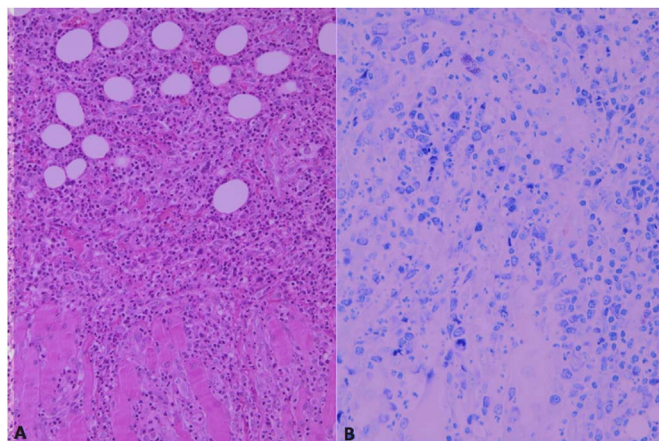


Fig. 3. A- Extremely dense inflammatory infiltrate of orbital fat (top) and ocular muscle (bottom) B-Mixed inflammatory cells: neutrophils, macrophages, plasma cells, and small lymphocytes with primary lymph follicle (right). No blasts, no granulomas or geographical necrosis.

The biopsy caused an inflammatory flare and subsequently the medial aspect of the eyelid became necrotic exposing the cornea.

Following biopsy of the lesion this gentleman's clinical condition deteriorated. The right upper eyelid became very painful. He described pain with ocular movement. He developed diplopia. The right eyelid swelling increased. Right relative proptosis of 3mm was measured. The movements of the right eye were restricted in all directions of gaze.

The lesion was found to have enlarged to involve the upper eyelid laterally and the orbit further medially upon repeat MRI scan of orbits. Treatment with intravenous vancomycin 1.5g twice daily and piperacillin and tazobactam 4.5 g three times daily had no effect. The patient's symptoms subsequently improved following three days treatment with intravenous methylprednisolone 1g daily.

With cessation of intravenous steroid therapy however this patient's condition again deteriorated. A second biopsy was performed. At attempted lid eversion the upper eyelid split at the junction of its medial third and lateral two thirds exposing the cornea. As previously, piecemeal removal of portions of the mass in an attempt to de-bulk it was completed.

This man's condition further declined thereafter. His vision deteriorated. Right proptosis and restriction of ocular movements further increased. Fundal examination showed choroidal folds and an inferior exudative retinal detachment. The ESR and CRP continued to rise.

He again received three days treatment with intravenous methylprednisolone 1g daily. Cyclophosphamide 100mg orally daily and prednisolone 60mg orally daily was subsequently prescribed. Cyclophosphamide was increased to 150 mg daily within 4 weeks. Improvement again occurred with reduced swelling and pain in the eye, and reduction in CRP and ESR.

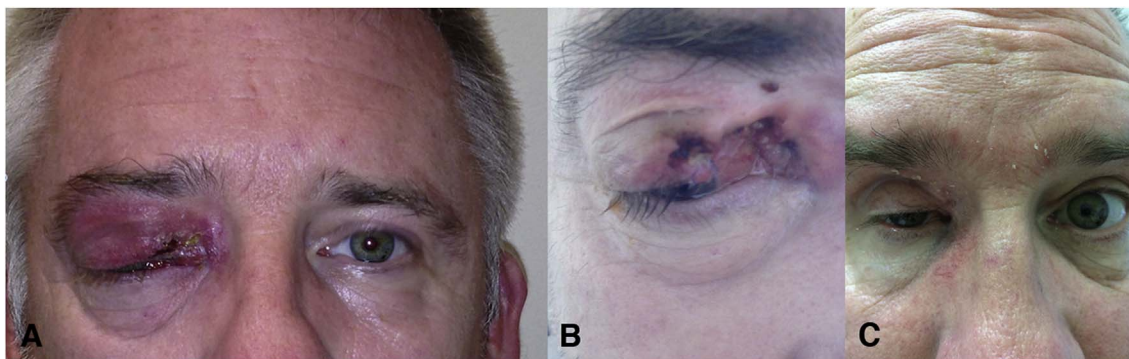


Fig. 2. A-Necrosis of eyelid post biopsy B- Reduction of inflammation post steroid and cyclophosphamide therapy C- Post operative repair.

Tapering of his oral prednisolone dose was later initiated. While receiving prednisolone 30mg daily the patient described the onset of a central scotoma in his left eye. Signs suggestive of a retinal vasculitis was apparent at fundal examination. Fundus fluorescein angiogram also provided evidence for the same. This resolved when the patient's corticosteroid dose increased to 40 mg daily.

A diagnosis of granulomatosis with polyangiitis (GPA) was made despite the lack of definitive histological evidence and negative ANCA. As his disease required high dose steroid therapy in addition to cyclophosphamide to maintain control, he received two intravenous infusions of rituximab 1g each, given 2 weeks apart, as a therapeutic trial. This was effective clinically and accompanied by resolution of MRI findings. Ultimately it permitted complete discontinuation of prednisolone and cyclophosphamide.

However a significant deficit in the medial portion of the eyelid remained with significant exposure of the cornea (Fig. 2B). Adhesion formation caused restriction of eye movements. Therefore reconstruction was planned. As previous biopsy had caused a major inflammatory reaction, he received two further infusions of rituximab 1g two weeks apart prior to the surgical intervention and peri-operative oral prednisolone 60 mg daily for 1 week. Eyelid reconstruction involved excision of anterior orbital scar tissue and division of adhesions between the eyelid and the globe. The posterior lamella of the eyelid and bulbar surface was covered with a buccal mucous membrane graft, reforming the superior conjunctival fornix. The anterior eyelid lamella was successfully re-opposed without the need for a skin graft (Fig. 2C). There was no reactivation of his inflammatory disease post operatively. Four years post operatively he remains symptom free. The patient provided written consent for publication of personal information including medical record details and photographs.

### 3. Discussion

Granulomatosis with polyangiitis (GPA) is a systemic vasculitis which typically affects the renal and respiratory systems, demonstrates ANCA positivity in 80–90% of cases and is characterised histologically by granulomatous inflammation, necrosis and vasculitis.<sup>1</sup> There is ocular involvement in approximately 50% of cases, but this is most often part of multisystem disease.<sup>2</sup> This case was difficult to diagnose, and confidence in the working diagnosis was due to a combination of biopsy results, evidence of retinal vasculitis and response to treatment. Based on clinical presentation, radiological and laboratory investigations the initial differential diagnosis for this patient included lymphoma, infection, sarcoidosis, GPA, IgG4-related disease and idiopathic orbital inflammatory disease. The consistent favourable response to immunosuppressive therapy made infection less likely. Development of retinal vasculitis in the contralateral eye on attempted steroid taper suggested a vasculitic process as the underlying pathologic mechanism. Although the characteristic histological features mentioned above were absent on biopsy, the mixed infiltrate and prominent neutrophilic component with neutrophilic microabscesses is often seen in GPA. Additionally, orbital histological specimens are less likely to show the classic pathological triad than other tissue specimens such as lung.<sup>3</sup> ANCA negativity is more common in limited GPA, being present as little as 32% of the time when disease is confined to the orbit.<sup>4</sup>

IgG4 related disease (IgG4-RD) was considered as a differential diagnosis as well as IgG4-RD/ANCA associated vasculitis overlap<sup>5</sup> since it is well known that several inflammatory conditions of the orbita, including GPA and non-specific inflammation, can cause increased IgG4 positive infiltrates of the orbita.<sup>6</sup> The ratio of IgG4 vs. IgG positive plasma cells in our case was 30%, with a maximum of 45 IgG4+ cells/high power field. Most recent studies have defined a threshold of 40% IgG4+ plasma cells for IgG4-RD<sup>7</sup> which was not reached in our patient. Moreover, IgG4-RD orbital involvement is mostly bilateral, which was not the case here, and with concomitant other organ involvement whereas the prominent neutrophilic component present in this case

again is not typical for IgG4-RD.<sup>8</sup> The polyclonal light chain pattern as well as molecular analysis of IgH argued against a lymphoproliferative disorder.

Cyclophosphamide and glucocorticoids are the mainstays of treatment for GPA, achieving remission in 70–90% of patients.<sup>9</sup> However cyclophosphamide has a number of potentially use-limiting side effects including cytopenias and cancer, and 50% of those who achieve remission will relapse within two years and may be exposed to the risks of repeated courses of high dose glucocorticoids.<sup>9</sup> Rituximab has emerged as an important treatment option in GPA. Rituximab is an anti CD20 monoclonal antibody that depletes B cells. Its efficacy was first demonstrated in uncontrolled trials in patients with refractory GPA, and there is now evidence that it may be as effective as cyclophosphamide at inducing remission.<sup>10,11</sup> Orbital masses in GPA are more likely to run a refractory course. In one series of 37 patients, only 8.1% had complete remission of the orbital mass, and 40% had disease progression with first line treatment, indicating the need for other options in this group.<sup>12</sup> Studies of rituximab in ocular GPA have shown variable rates of efficacy, but resulted in a treatment response in the majority.<sup>13,14</sup>

The decision to undergo reconstruction was a difficult one because of the concern about flare-up of the orbital inflammatory disease. Surgery is a last resort treatment option in GPA, and in ocular GPA is usually performed to debulk the inflammatory mass in the orbit where there is proptosis or optic nerve compression, or enucleations in cases of refractory disease with severe pain.<sup>1,12</sup> In the case of our patient, biopsy alone had caused a major inflammatory flare which led to necrosis of the medial eyelid and the resulting defect. Reconstruction of eyelid defects has not been reported, and reports of reconstructive surgery in GPA are limited. However reconstruction of saddle nose deformities have been shown to be effective and safe in a small cohort of patients so long as disease is in remission.<sup>15</sup> Hashem et al. recently reported the first facial vascularized composite allotransplantation in a patient with GPA, in whom disease remission was achieved with rituximab. The surgery has been successful at one year post transplant.<sup>16</sup> To our knowledge this is the first report of successful reconstruction of an ocular defect secondary to GPA, an addition to limited experience of surgery in this disease.

### Patient consent

The patient provided written consent for publication of personal information including medical record details and photographs.

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### Conflicts of interest

The following authors have no financial disclosures; GK, KH-O, TF, EM, NM, EK, HM, GM.

### Authorship

All authors attest that they meet the current ICMJE criteria for authorship.

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### Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.ajoc.2018.03.014>.

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