Rituximab For Remission In Relapsing Anca Negative Retro Orbital Wegener's Granulomatosis

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Citation

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Abstract

We present a follow-up on a previously published case of a 59 year-old female diagnosed with ANCA negative limited Wegener's Granulomatosis(WG) of the right orbit with history of Graves ' disease who presented with exophthalmos. Despite treatment with steroids and cyclophosphamide, patient had a relapse while steroids were being tapered. She was then treated with IV Rituximab with remission and resolution of her symptoms. She is currently doing well on maintenance therapy with methotrexate. Rituximab is a monoclonal anti-CD20 antibody effective in treatment of ANCA associated vasculitis including systemic WG. Our case shows Rituximab may be a therapeutic option in the treatment of ANCA negative retro orbital WG in patients who failed treatment with cyclophosphamide.

INTRODUCTION

Wegener's Granulomatosis (WG) is characterized by granulomatous inflammation involving the respiratory tract and kidneys and necrotizing vasculitis of small to medium sized vessels (5). The cause of WG is not known. WG is typically associated with positive antineutrophil antibodies (ANCA). However a small proportion of patients do not have detectable antineutrophil antibodies (ANCA negative) and is seen in limited WG sparing the kidneys. Limited ophthalmic WG can cause severe inflammation of the ocular and periocular tissues which can result in loss of vision (10). Cyclophosphamide and high dose corticosteroids have been used successfully in the treatment of severe ophthalmic WG disease. In ANCA positive refractory ocular WG the successful treatment with Rituximab has been reported (3). We present a follow-up on the previously published case report "Exophthalmos as a presenting manifestation of limited Wegener's Granulomatosis in a patient with prior Graves' Disease" (6). The patient was diagnosed with ANCA negative retro orbital WG who initially responded well to combination treatment with cyclophosphamide and steroids as previously reported but later relapsed. She was then treated with Rituximab with resolution of her symptoms.

CASE REPORT

A 59 year old female with a history of Graves' disease diagnosed over 20 years presented to her ophthalmologist with new onset right eye redness, pain, dryness and worsening exophthalmos (6). MRI of the brain and orbits was obtained which showed a soft tissue mass behind the right orbit. Biopsy of the mass showed "trans mural inflammation with fibrinoid necrosis consistent with necrotizing vasculitis and lymphocytic infiltration consistent with Graves' disease" (6). ANCA was negative. She was diagnosed with limited retro orbital Wegener's granulomatosis in the setting of Graves' disease and treated initially with high dose prednisone and cyclophosphamide followed by methotrexate (6).

Initial MRI of brain and orbit revealed enhancement of soft tissue intimately associated with right optic nerve sheath (Fig 1). Subsequent MRI brain and orbit obtained in Sep 2009 following treatment with cyclophosphamide and steroids showed increase in size of infiltrative mass compressing the right optic nerve at the right orbital apex (Fig 2). Given the clinical worsening of symptoms and worsening of the lesion per MRI brain and orbit despite treatment with cyclophosphamide and steroids, Rituximab was started initially as 2 doses of 1gm each, 2 weeks apart. Patient received 2 courses of Rituximab over the last one year with improvement in symptoms. We were able to taper off her prednisone and currently she continues to do well on methotrexate. Repeat MRI Brain and orbits obtained in Oct 2010 showed evidence of significant decrease in the abnormal infiltrative mass in the right orbital apex (Fig 3).

Figure 1

Figure 1: MRI of brain and orbit showing enhancement of soft tissue associated with right optic nerve sheath

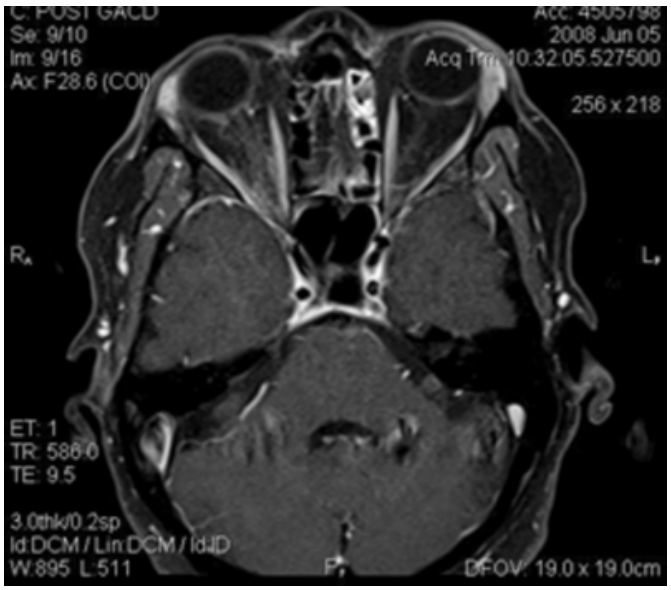


Figure 2

Figure 2: MRI of brain and orbit showing abnormal infiltrative mass in the right orbital apex increased in size and compressing right optic nerve

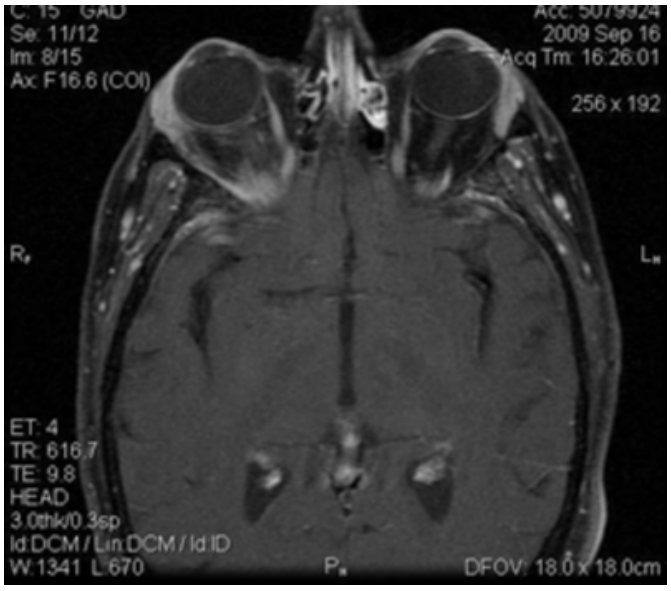
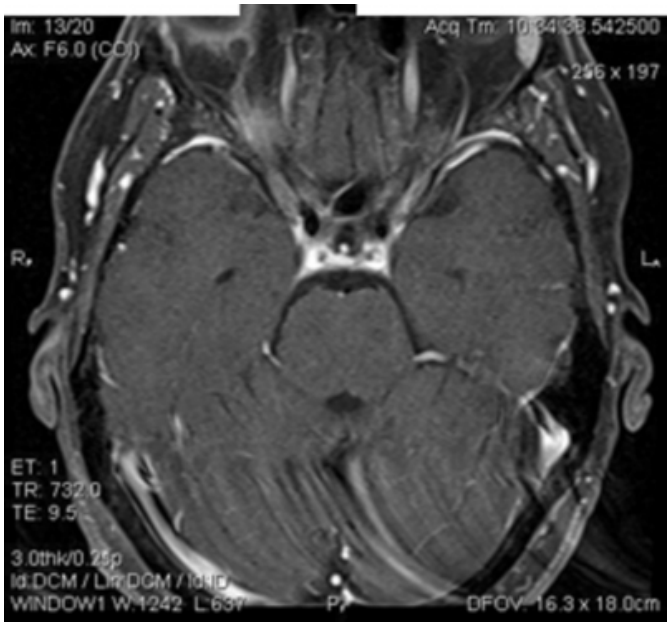


Figure 3

Figure 3: MRI of brain and orbit showing interval decrease in the previously seen abnormal infiltrative mass in the right orbital apex



DISCUSSION

WG is a granulomatous necrotizing vasculitis mainly affecting the upper and lower respiratory tracts and kidneys (12). Ocular symptoms of keratitis, conjunctivitis, scleritis, episcleritis, uveitis, optic neuritis and retro orbital pseudo tumors with proptosis have been reported in 58% of patients with WG and can cause significant visual morbidity in 8% to 17% of cases (10). The conventional treatment in ophthalmic WG is high dose steroids and cyclophosphamide and maintenance with methotrexate as well as azathioprine (13, 14). However in patients with refractory limited ophthalmic WG, treatment options are not very clear.

Rituximab is an antiCD20 B cell monoclonal antibody and has been used in the treatment of ANCA associated systemic WG. In previous studies, biopsy samples of endonasal specimens from patients with WG have shown follicle like B lymphocytic infiltrations within the granulomatous lesions (7). It is felt these B cells may initiate the inflammatory process by production of antibodies (8). Rituximab depletes the B cells responsible for ANCA production. The RAVE Trial has demonstrated that "Rituximab therapy was not inferior to daily cyclophosphamide therapy for induction of remission in severe ANCA associated vasculitis and may be superior in relapsing disease"(5).

A review of literature found a few reports of the use of Rituximab in patients with ophthalmic manifestations of WG

refractory to cyclophosphamide treatment. The authors of these reports suggested that the response in ophthalmic disease is poor because of the "fibrotic nature of granulomas " in WG especially in retro orbital involvement (11). However per other studies, Rituximab was found to be effective in treating refractory ANCA positive ophthalmic WG resulting in sustained remission (3).

The way in which B cell depletion works in ANCA negative cases is not well understood. B cells are also effective antigen presenting cells and activators of T cells and may possibly contribute to disease by this mechanism in the absence of detectable auto antibodies (9).

The previous published studies showed the effectiveness of Rituximab in ANCA positive refractory ophthalmic WG. This case is unique in that our patient had ANCA negative retro orbital (ophthalmic) WG who relapsed following treatment with cyclophosphamide but responded well to Rituximab.

CONCLUSION

Our case shows that Rituximab may be considered a therapeutic treatment option in achieving remission in ANCA negative retro orbital WG in patients who have failed treatment with cyclophosphamide.

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