CASE REPORT

Successful use of Rituximab in a patient with recalcitrant multisystemic eosinophilic granulomatosis with polyangiitis

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Accepted 29 April 2015

SUMMARY

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare eosinophil-rich disorder characterised by necrotising granulomatous inflammation affecting small to medium sized vessels. Extrapulmonary manifestations can be life-threatening when heart, central nervous system (CNS), gastrointestinal tract or kidneys are affected. We describe a case of a 56-year-old woman with a long-standing history of asthma, who presented with an acute sudden painless loss of vision after she had been recently diagnosed with EGPA and induced with pulse steroids and cyclophosphamide. The patient had a complicated hospital course with multisystemic involvement of active vasculitis, involving heart, kidneys, muscles, eyes and CNS. The patient's devastating condition responded remarkably to Rituximab. The role of Rituximab in EGPA is not yet proven. Few cases are reported in the literature about the role of Rituximab in EGPA, of which only one described retinal artery occlusion as a presentation of a recently treated patient with EGPA.

BACKGROUND

The role of Rituximab in eosinophilic granulomatosis with polyangiitis (EGPA) is not yet proven. Few cases are reported in the literature about the role of Rituximab in EGPA, of which only one described retinal artery occlusion as a presentation of a recently treated patient with EGPA. Our report offers a rare presentation of a rare disease with multisystemic involvement of active vasculitis and resistance to first-line treatment, with a clinical response to Rituximab, an as yet unproven drug.

CASE PRESENTATION

A 56-year-old Caucasian woman with a long-standing history of asthma presented with a 1-week history of bilateral lower extremity pain, retrosternal chest pain and loss of appetite. Investigations demonstrated diffuse patchy lung infiltrates, pronounced eosinophilia (45%), new onset right foot drop and a positive myeloperoxidase antibody of 37.8 (normal <1.0). A diagnosis of EGPA was made. The patient received pulse methylprednisolone (1 g/day) for 3 days and was then switched to prednisone 60 mg/day (1 mg/kg).

The patient was readmitted 2 days after her discharge with worsening dyspnoea and diffuse patchy pulmonary infiltrates. Infectious work up was negative. Her eosinophil count had increased to 15% (normal <5%). Her prednisone dose was increased

to 80 mg/day and cyclophosphamide 75 mg/day (1.5 mg/kg) was initiated. With treatment, the foot drop improved, the lung infiltrates cleared and the eosinophil count normalised. Her prednisone was tapered to 70 mg/day over 2 weeks.

She was clinically improving until 2 weeks later when she had sudden left painless central greying in her vision alternating with completed blackness. On presentation to the hospital, she regained vision in the peripheral fields only.

INVESTIGATIONS

Investigations revealed left central retinal artery occlusion. The patient's eosinophil count was elevated at 12%, erythrocyte sedimentation rate (ESR) was 60 mm/h and C reactive protein (CRP) was 62. Her prednisone dose was increased to 150 mg/day (2 mg/kg) and the cyclophosphamide to 100 mg/day (2 mg/kg). She continued to have episodic left-sided vision loss requiring high-dose methylprednisolone 500 mg/day for 3 days. She also developed severe bilateral thigh tenderness with a total creatine kinase level of 350 U/L (normal <10–170 U/L). MRI of the thighs demonstrated extensive myositis of the vastus medialis and lateralis muscles bilaterally (figure 1A). Investigations also noted a troponin level of 0.29 ng/mL (normal <0.1 ng/mL). A cardiac MRI revealed extensive myocardial enhancement with mild cardiomyopathy (ejection fraction 53%; normal >60%) (figure 1B). The patient developed proteinuria (urinalysis with 2+ protein; 24 h urine protein/creatinine ratio of 1.1 g) and haematuria (3–4 red blood cells/high power field (hpf) with 2 dysmorphic red blood cells observed). Renal biopsy demonstrated focal segmental necrotising glomerulonephritis with dense eosinophilic infiltrates (>70 eosinophils/hpf) (figure 2).

TREATMENT

The patient's Birmingham Vasculitis Activity Score 2003 was 32. Her 1996 FFS (five-factor score) was 2, predicting a 5-year mortality rate of 46%. Given her active multisystemic vasculitis despite aggressive treatment with pulse methylprednisolone, high-dose prednisone and cyclophosphamide, Rituximab infusions were initiated at 375 mg/m² weekly for a total of four infusions. Prednisone 150 mg/day and cyclophosphamide 100 mg/day were also continued. After treatment with Rituximab, the patient improved, with resolution of her myositis, nephritis and pulmonary

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To cite: Najem CE, Yadav R, Carlson E. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-206421

Figure 1 Myositis of the muscles. (A) MRI of the thighs demonstrating a focal oedema in the left vastus medialis muscle (arrow) and right vastus lateralis muscle (curved arrow), with oedema of the intermuscular fascia; and (B) cardiac MRI demonstrating anterioseptal punctuate enhancement (arrow) with subendocardial enhancement (curved arrow) of the inferior wall base.

infiltrates. Her left central retinal artery occlusion improved remarkably as well: she regained vision in the peripheral and central fields. Her ESR, CRP and eosinophil count normalised. On discharge, she was continued on prednisone 150 mg/day and cyclophosphamide 100 mg/day, which were being tapered over a time period 4–5 months. In the setting of a strong outpatient immunosuppressive regimen, trimethoprim-sulfamethoxazole was initiated for *Pneumocystis jirovecii* pneumonia prophylaxis. In order to prevent cyclophosphamide-induced cystitis, the patient was instructed about the importance of drinking liberal quantities of fluid to decrease the bladder's exposure to acrolein. Regular and frequent laboratory evaluations were planned to screen for bone marrow toxicity and kidney impairment. Further, the patient was also instructed about cognitive changes and psychosis that might occur in patients on high-dose glucocorticoids, and appropriate psychological support was provided. Regular and frequent physical examinations, and monitoring of blood pressure, blood glucose and white cell counts was planned. The concomitant use of non-steroidal anti-inflammatory agents was prohibited. Vitamin D₃ and calcium supplements were initiated.

Repeated Rituximab infusions are anticipated in the future.

DISCUSSION

EGPA is a rare eosinophil-rich disorder characterised by necrotising granulomatous inflammation affecting small to medium sized vessels characterised by asthma, pulmonary infiltrates and hypereosinophilia.^{1–2} Extrapulmonary manifestations can be life-threatening when heart, central nervous system, gastrointestinal tract or kidneys are affected.^{1–3} EGPA is associated with antineutrophil cytoplasm antibody (ANCA) in less than 40% of patients.^{1–3}

Less than 10% of patients with ANCA-associated vasculitis (AAV) are refractory to standard therapy,⁴ and only one case of refractory EGPA with central retinal artery occlusion has been reported.⁵ Most studies describing the efficacy of inducing remission in EGPA with Rituximab are from case reports and case series alone^{6–7} or extrapolated from randomised trials studying other types of AAV.⁸

For remission induction, randomised trials have reported similar remission rates with Rituximab and cyclophosphamide, and Rituximab is now an approved alternative to cyclophosphamide in severe AAV.^{9–12} Moreover, Rituximab might be superior to the standard therapy with cyclophosphamide for remission induction in severe relapsing AAV.⁹ The long term results of the RAVE trial (Rituximab vs Cyclophosphamide for AAV) indicated

Figure 2 Kidney biopsy-light microscopy revealing (A) a dense eosinophilic infiltrate in the subcapsular area with >70 eosinophils/hpf (high power field); and (B) a glomerulus with segmental necrosis, karyorrhectic debris and fibrinoid necrosis (arrow).

that for the treatment of severe AAV, a single course of Rituximab, at a dose of 375 mg/m² weekly for 4 weeks, combined with glucocorticoids is not inferior to 18 months of the conventional regimen of glucocorticoids and cyclophosphamide followed by maintenance therapy with azathioprine.¹⁰ This finding is also consistent with the results from many reported case series and cohort studies of refractory microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA), based on which Rituximab has emerged as the de facto standard of care for refractory MPA and GPA, extrapolating its promising results in patients with refractory EGPA.¹³

Rituximab has been (and is being) investigated in order to further improve disease-related outcomes by reducing refractory disease, relapse and chronic organ damage, and as a potent corticosteroid-sparing agent leading to progressive tapering of corticosteroids, and possible complete withdrawal.^{9–12} Another important expectation from Rituximab therapy is reduced toxicity compared with the standard cyclophosphamide and high-dose glucocorticoids regimen, particularly lower risk of infections, malignancies and infertility.¹¹ However, Rituximab has been associated with a minimal risk of hepatitis B reactivation, progressive multifocal leukoencephalopathy following JC virus reactivation and late-onset neutropenia in 5% of patients.¹⁴

In EGPA, limited data suggest that successful remissions can be induced by Rituximab in both ANCA-positive and ANCA-negative disease.^{7 15} Twelve cases were reported in the literature documenting refractory EGPA to standard remission induction therapy with cyclophosphamide, glucocorticoids (and immunoglobulins sometimes), but responsive to Rituximab therapy.¹⁶ Reported involved organs were kidneys, heart, skin, central or peripheral nervous system and lungs.^{15–21} A recent retrospective multicentre study including 41 patients with EGPA treated with Rituximab between 2003 and 2013, demonstrated remarkable response to Rituximab in cases of refractory (37%), relapsing (51%) and new onset EGPA (12%).²² By 6 months, 83% improved with remission in 34% and partial response in 49%, and by 12 months, 49% were in remission and 39% had a partial response. Interestingly, prednisone doses were successfully decreased in all 41 patients by 6 and 12 months.²²

Learning points

- ▶ Less than 10% of patients with antineutrophil cytoplasm antibody-associated vasculitis are refractory to standard therapy.
- ▶ Organs such as the central nervous system, heart or kidneys, being affected can be life-threatening.
- ▶ Only one case of refractory eosinophilic granulomatosis with polyangiitis (EGPA) with central retinal artery occlusion has been reported.
- ▶ Most studies describing the efficacy of inducing remission in EGPA with Rituximab are from case reports.
- ▶ Rituximab is a promising drug that might change the pattern of EGPA from a chronic relapsing disease to a chronic remitting disease.

In conclusion, Rituximab might be a safe and important alternative to standard remission induction regimens in EGPA, both for refractory and relapsing patients, and also for newly diagnosed patients in whom traditional cytotoxic drugs are contraindicated. Prospective randomised trials are needed to confirm its safety and efficacy in patients with refractory and relapsing EGPA.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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