

# Granulomatosis polyangiitis associated with meningeal involvement: response to rituximab therapy after failure of cyclophosphamide

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## SUMMARY

Wegener's granulomatosis or granulomatosis polyangiitis associated (GPA) is a granulomatous inflammation of the upper and lower respiratory tracts associated with necrotising vasculitis of small and medium-sized blood vessels and, frequently, necrotising glomerulonephritis.

We describe the case of a 37 year old female patient presenting with upper respiratory tract involvement, chronic rhinosinusitis with green secretions, and bilateral hypoacusia. Ten months later, she suffered occipital headache and two episodes of lipothymia associated with nausea, photophobia, faintness with visual blurring. Magnetic resonance imaging (MRI) revealed aseptic meningitis. The patient was treated with steroids and cyclophosphamide without any effect on the neurological symptoms which, however, greatly improved after subsequent treatment with rituximab as confirmed by means of cerebral MRI.

Rituximab is an optimal means of treating cyclophosphamide-resistant patients with GPA associated with meningeal involvement.

**Key words:** *Granulomatosis polyangiitis associated, Rituximab.*

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## ■ INTRODUCTION

Wegener's granulomatosis (WG) or granulomatosis polyangiitis associated (GPA) is a granulomatous inflammation of the upper and lower respiratory tracts associated with necrotising vasculitis of small and medium-sized blood vessels and, frequently, necrotising glomerulonephritis (1). The introduction of glucocorticoid and cyclophosphamide (CYC) treatment about thirty years ago (2) was a major step forward in the management of the disease, which had been almost invariably fatal until then. However, treatment is still unsatisfactory because about 25% of the patients treated with alkylating agents or methotrexate (MTX) do not achieve complete disease remission (3-5), relapses occur in 15-45% (6, 7), and 20-50% develop severe treatment-related adverse events (3, 5).

Consequently, many new treatments have been evaluated in an attempt to improve efficacy and reduce the toxicity associated with the prolonged use of alkylating agents (5, 8, 9).

Rituximab (RTX), a chimeric monoclonal anti-CD20 antibody that selectively depletes B lymphocytes for prolonged periods and is used to treat B cell lymphomas, has recently been used to treat rheumatoid arthritis and various refractory autoimmune diseases (10).

## ■ CASE REPORT

In November 2008, a 37 year old female weighing 101 kg was admitted to our Unit because of mild fever, arthralgia, diffuse abdominal pain, bilateral hypoacusia, right-sided otalgia and cephalgia.

Her medical history included a diagnosis of

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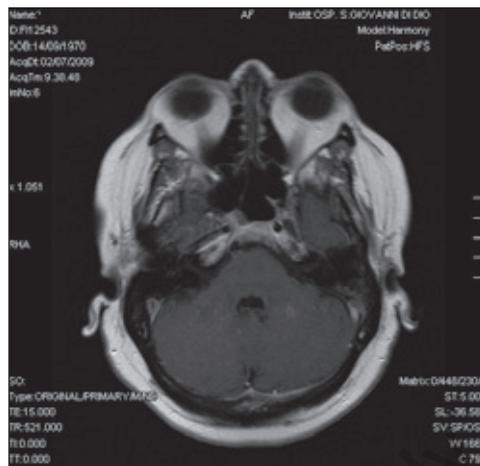
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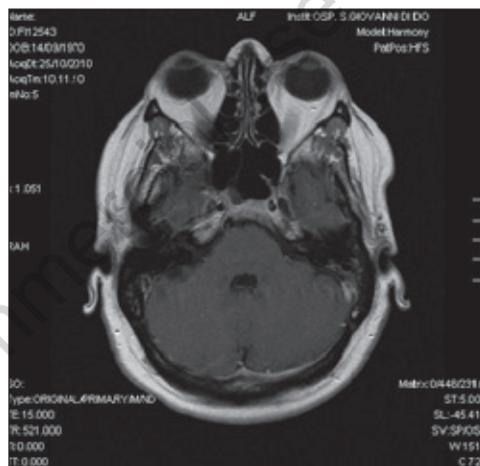
of hypertension in May 2008, and an acute myocardial infarction treated by means of percutaneous transluminal coronary angioplasty and the placement of a posterior intraventricular artery stent in August 2008. In September 2008, she suffered from blindness in the right eye, and an ocular fundus test revealed occlusion of the central retinal artery with papillitis. The patient reported chronic rhinosinusitis with green secretions, cultures of which proved to be positive for *Staphylococcus aureus*. Magnetic resonance imaging (MRI) revealed inflammation of the middle ear bone and sinus opacity. Nasal mucosal biopsy showed a granulomatous inflammation in the wall of arteries or arterioles, in perivascular and extravascular sites as defined by the American College of Rheumatology criteria (11). Laboratory tests showed an erythrocyte sedimentation rate of 78 mm/h (normal value (n.v.)  $\leq 20$  mm/R), C-reactive protein 3.4 mg/dL (n.v.  $\leq 0.5$  mg/dL), leukocytosis 13,450 white cells/mm<sup>3</sup> and anti-proteinase 3 (anti-PR3) measured by means of immunofluorescence (Euroimmun, Lubbeck, Germany) and by combo EIA index (Orgentec Diagnostika GmbH, Mainz, Germany) positive with title 1:160. A diagnosis of limited GPA was made and the patient was treated with prednisone 75 mg/day plus CYC 2 mg/kg, discharged, and then followed-up every three months. Ten months later, in October 2009, the patient suffered from persistent occipital headache and two episodes of lipothymia associated with nausea, photophobia, faintness and visual blurring. Brain MRI revealed an increased gadolinium signal indicating dural thickening in the tentorium of the cerebellum (Fig. 1).

The patient was treated with pulsed methylprednisolone 1 g/day for two consecutive days and pulsed CYC 1 g every 15 days, which was stopped after 3 months due to the increase of headache associated with nausea and photophobia and possible adverse events due to the cumulative dose of CYC (6 g).

A screening for hepatitis B and C virus, tuberculosis including Mantoux, Quantiferon tests and chest radiography was negative.



**Figure 1** - MRI: dural thickening in the tentorium of the cerebellum.



**Figure 2** - MRI: decrease in the dural thickening in the tentorium of the cerebellum.

In January 2010, the patient was treated with prednisone 50 mg/day combined with MTX 15 mg/week and RTX 700 mg (375 mg/m<sup>2</sup>) per month for six months, and then every three months.

Two months later, the neurological symptoms improved with completed resolution at fourth month. MRI in October 2010 revealed a decrease in the dural thickening in the tentorium of the cerebellum (Fig. 2). Based on re-population of B lymphocytes, in particular by mean of flow-cytometry we evaluated the levels of naïve and memory CD27, the panels of B (CD20, CD38, CD19), and we re-treated the patient every six-months.

## ■ DISCUSSION

Chronic meningitis is a rare complication of GPA. It was detected in only two out of 324 GPA patients attending the Mayo Clinic in Rochester (12, 13) and in none of the patients described in other large series (14). Furthermore, a search for individual case reports revealed only 46 patients (15). Headache is the most frequent symptom associated with chronic meningitis but, as it is also associated with GPA (due to chronic sinusitis or orbital disease), meningeal involvement may remain unrecognised for a long time although, later in the course of the disease, most of patients develop other neurological abnormalities. The most frequently observed MRI finding is diffuse (followed by focal) dural thickening, usually involving the tentorium; the leptomeninges are affected in only a minority of cases. Although 62.9% of the patients are positive for anti-neutrophil cytoplasmic antibodies (ANCA), a cytoplasmic staining is observed in only 37.1% (16).

The majority of patients with GPA and meningeal involvement have been treated with high-dose corticosteroids and immunosuppressants. CYC is the most frequently used drug and, like MTX, leads to successful results. Every consensus suggests that organ involvement in GPA should be treated promptly and aggressively and, on the basis of the published data, high-dose of corticosteroids associated with CYC or MTX should be used for treating meningitis in GPA patients (15).

RTX is a chimeric monoclonal antibody against CD20, a B cell marker that is expressed from the pre-B to the mature phase of B cell development, but is not expressed in pro-B cells, memory cells, plasma cells, or antibody-secreting B cells. RTX binds CD20 in B cells and induces cell death by means of a still unknown mechanism, although *in vitro* experiments have shown that antibody-dependent cytotoxicity, complement-mediated B-cell lysis, apoptosis, and sensitisation to cytotoxic agents or corticosteroids may all play a role.

RTX has been used as rescue medication in patients with refractory GPA or contra-

indications to CYC. About 100 published cases of GPA have been treated with RTX (17), which seems to be effective in treating its vasculitic manifestations such as pulmonary capillaritis and necrotising glomerulonephritis. However, it is still unclear whether RTX is equally effective in treating the necrotising granulomatous manifestations of GPA, such as orbital pseudotumours or subglottic stenosis (18). The Rituximab for ANCA-associated Vasculitis (RAVE study) (19), which involved 197 ANCA-positive patients with GPA or microscopic polyangiitis, found that RTX therapy was not inferior to daily CYC treatment in inducing remission and that it may be superior in relapsing disease. The results showed that 34/51 patients in the RTX group (67%) reached the primary end point against 21/50 patients in the control group (42%); moreover, only one patient in the RTX group had meningeal involvement. The Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis (RITUXVAS) is a randomised controlled trial that included 44 patients with new diagnosed ANCA-associated vasculitis and renal involvement, who were randomised 3:1 to receive a standard glucocorticoid regimen plus four intravenous administrations of RTX 375 mg/m<sup>2</sup> per week, with two intravenous CYC pulses given concomitantly with the first and third RTX infusion, or the same standard glucocorticoid regimen plus intravenous CYC pulses for 3-6 months followed by oral azathioprine. The 12-month rate of sustained remissions (defined as a Birmingham vasculitis activity score of 0 for six months) was similar in both treatment arms (20).

Despite these important trials, a recent study involving 59 patients found that the overall response rate to RTX was high in patients with granulomatosis with polyangiitis (61.3% experienced remission or improvement), but the patients with pachymeningitis or orbital involvement had the same rate of refractory disease (33.3%) (21). The possible differences in term of response to RTX therapy among orbital involvement linked to granulomatous lesion

and pachimeningitis linked at vasculitis lesion are described (18).

A total of 7 cases that showed the efficacy of RTX in meningitis within GPA are described (22-24).

Patients with active vasculitis have a lower proportion of Bm1 cells that may indicate activated B cells, whereas patients in remission have higher proportions of CD25+ (the  $\alpha$ -chain of the interleukin 2 receptor) and CD86+ (co-stimulatory molecule) B cells. This suggests that B cells may play a regulatory role in the pathogenesis of GPA (25). ANCA's induce the release of BLYS from activated neutrophils that support B cell survival *in vitro*, and the presence of BLYS in the serum of patients with active disease and after B cell depletion suggests that it plays a role in B cell activity and survival (26). All of these findings support the use of RTX in patients with WG, and may explain possible post-treatment relapses. To the best of our knowledge, ours is the first case showing an improvement in neurological symptoms confirmed by means of cerebral MRI in a patient with WG and meningeal involvement after treatment with RTX combined with MTX and prednisone.

In conclusion, RTX therapy is an optimal means of treating CYC-resistant patients with WG associated with meningeal involvement. Our results justify its use in a large clinical series of such patients in order to confirm its efficacy.

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