Pachymeningitis and cerebral granuloma in granulomatosis with polyangiitis: is rituximab a promising treatment option?

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ABSTRACT

Granulomatosis with polyangiitis (GPA) is a rare immune-mediated disease characterized by granulomatous inflammation involving upper and lower respiratory tract, kidneys and peripheral nervous system. However, central nervous system involvement is uncommon and frequently refractory to classical therapy. Rituximab has emerged as promising alternative, but published reports are scarce. We report a case of pachymeningitis and cerebral granuloma in a patient with a history of severe generalized GPA, treated with rituximab. This case illustrates the complexity of the management of neurologic manifestations and provides insight into the potential utility of rituximab in this condition.

Keywords: Pachymeningitis; Granulomatosis with polyangiitis; Rituximab; Cerebral granulomas

INTRODUCTION

Central nervous system (CNS) manifestations have been described in 7-11% of all cases of granulomatosis with polyangiitis (GPA)[1-4]. Global headache is the most frequent and usually the first symptom of GPA-related pachymeningitis, however it can be present due to chronic sinusitis or orbital disease. Therefore, meningeal involvement can remain unrecognized for a long time. Ataxia, cranial neuropathy, seizures, diplopia, ophthalmoplegia, monolateral proptosis and psychiatric syndromes are less common[1,2,5,6].

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CNS manifestations are often associated with a refractory course disease with failures of classic treatments, including glucocorticoids and cyclophosphamide (CYC)[7]. Treatment of granulomatous CNS is still a challenge and may result in significant irreversible organ damage if disease activity control is not promptly achieved[8].

Rituximab, a monoclonal anti-CD20 chimeric antibody, has successfully been used to treat patients with GPA, refractory orbital granuloma in GPA or other ANCA-associated systemic vasculitis[9-11]. However, it is still unclear whether rituximab is effective in treating CNS involvement in GPA, manifested by necrotizing granulomata and pachymeningitis[12,13].

CASE REPORT

A 50-year-old male was admitted to our Rheumatologic Unit due to a two-week history of severe and persistent headache, nausea, ataxic gait, behaviour changes and periods of somnolence.

He had a nine-year history of severe generalized GPA with multiple organ involvement. It had gradually extended to affect the upper respiratory tract with nasal ulcers, bony and cartilage destruction resulting in saddle nose deformity; the ocular system with orbital pseudotumor resulting in left proptosis and amaurosis; the lung parenchyma with infiltrates and nodules; the heart with an atrioventricular block (pacemaker implant); the genitals with scrotum granulomas and the peripheral nervous system (sensitive mononeuropathy of peroneal nerve).

He was treated in the past with high doses of glucocorticoids, oral CYC (1440 mg/kg of cumulative dose) and azathioprine (maintenance of remission) with good control of disease activity. Due to a late intolerance to

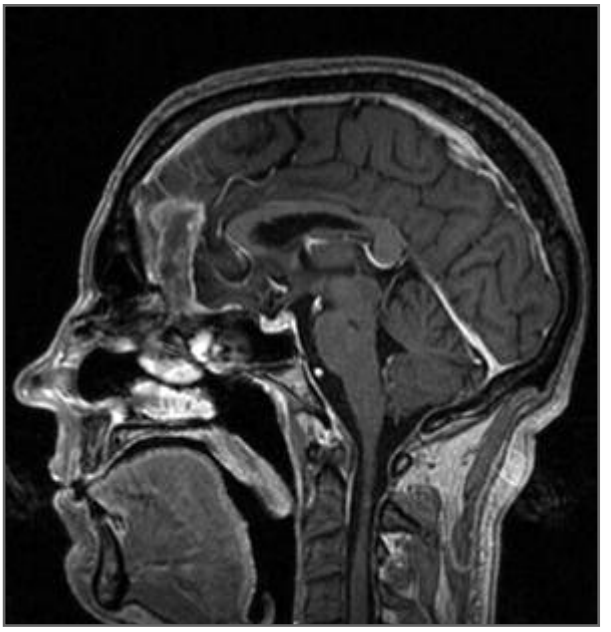

FIGURE 1. T1W gadolinium-enhanced MRI (before rituximab): diffuse dural enhancement and cerebral granulomas

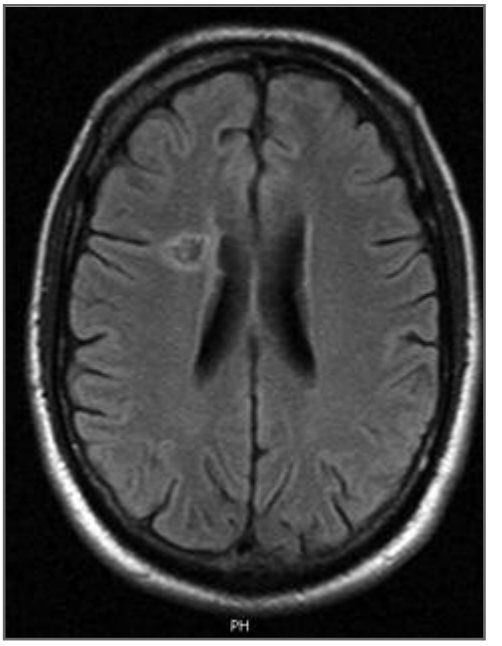

FIGURE 2. T1W gadolinium-enhanced MRI (before rituximab): diffuse dural enhancement and cerebral granuloma

azathioprine, it was switched to methotrexate.

When admitted to our department, the patient was on a daily maintenance therapy of prednisolone (5 mg/day) and methotrexate (7.5 mg/week, reduced from an initial dose of 15 mg/week due to nausea and vomiting). His family described a two-week history of morning headaches, behavioural changes with inconsistent speech, erratic ideas and a refusal to fulfil the treatment regimen. Throughout his stay in our department, he presented uninhibited behaviour, inversed sleep pattern, confusion and auditory hallucinations. Neurological examination revealed generalized hyperreflexia, predominantly in the left side, and discrete ataxic gait.

Laboratory studies showed an erythrocyte sedimentation rate (ESR) of 35 mm/h (normal value < 20 mm/h), C-reactive protein (CRP) of 2.57 mg/dL (normal value < 0.5 mg/dL), leucocytes 6.9 x 10^6 /L and c-ANCA positive antibody, with anti-proteinase 3 (PR3) of 4.6 U/mL (positive if > 3.0 U/mL). Mantoux test (> 15mm) and interferon-gamma release assay (IGRA) were positive. No signs of active tuberculosis were found on chest X-ray and high resolution computed tomography. Cytology, microbiology analysis and electrophoretic profile of the cerebrospinal fluid were normal. Urine and blood cultures were negative, including for *Mycobacterium tuberculosis* infection. The screening for HIV and hepatitis B and C was negative. Electroencephalography was normal. Cranial computed tomography, cerebral angiography and cerebral single photon emission computed tomography (SPECT) with HMPAO-Tc99m were normal. Brain magnetic resonance imaging (MRI) showed diffuse dural enhancement and small, ill-defined, nonenhancing high signal areas measuring 5-20mm in several locations (Figure 1 and 2).

At this time the Birmingham vasculitis activity score (BVAS) was 27 points.

Intravenous immunoglobulin (400 mg/Kg/day) was administered for 5 days and the patient started methylprednisolone (64 mg/day) with progressive tapering. A 6-month course of isoniazid (300mg/day) and pyridoxine (150mg/day) for latent tuberculosis infection was also started. Rituximab was prescribed with a regimen of four weekly infusions of 375 mg/m^2 of body surface area. Clinical symptoms started to improve gradually after the third rituximab administration.

After six months, the patient was asymptomatic, with complete resolution of headache, behavioural changes and ataxic gait. PR-3 ANCA was persistently negative; ESR and CRP were normal (8 mm/h and 0.10 mg/dL, respectively). Repeated brain MRI showed a marked improvement of the cerebral granuloma, although still present in brain parenchyma (Figure 3 and

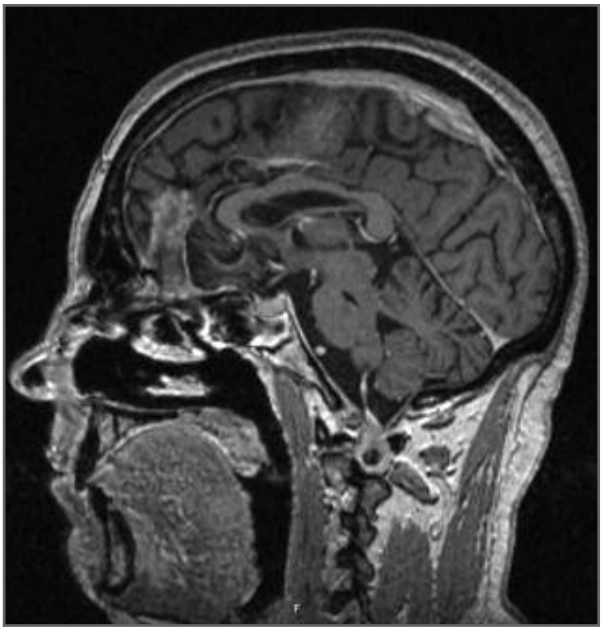

FIGURE 3. T1W gadolinium-enhanced MRI (6 months after rituximab)

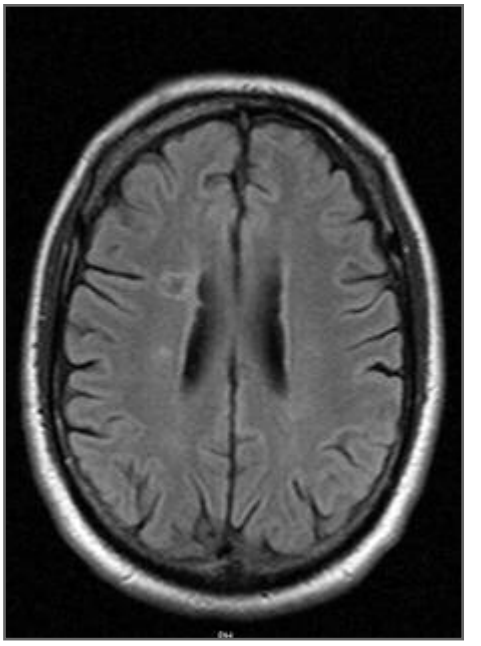

FIGURE 4. T1W gadolinium-enhanced MRI (6 months after rituximab)

4). The BVAS score at this time was 3 points. A second infusion of rituximab for maintaining remission (500mg at days 0 and 14) was administrated.

Twenty-eight months after the last administration of rituximab the patient is free of immunosuppressive drugs and remains asymptomatic.

DISCUSSION

In our case, the patient predominantly presented headache and behaviour changes with discreet changes in neurological examination and laboratory studies. As he had a long history of immunosuppression, we needed to rule out other disorders such as atypical meningioma, lymphoma, tuberculosis or fungal infection. Cerebral or meningeal biopsy was not performed because chronic meningitis had been excluded with cerebrospinal fluid examination and may lead to serious complications. Brain MRI confirmed the CNS involvement of GPA. The most common findings on MRI are dural thickening, usually involving the tentorium; leptomenges are affected in a minority of cases[6].

Combination therapy with corticosteroids and CYC was the backbone of all regimens for induction of remission[2]. Most patients with GPA and meningeal involvement have been treated with high doses of corticosteroids and CYC, and this treatment must be promptly administered[5]. In the past, our patient had been submitted to high CYC cumulative doses, so, we decided to use rituximab to treat pachymeningitis and cerebral granulomas.

In five large series of GPA, pachymeningitis was reported in only two out of 662 patients[1]. In other two series, no cases were reported in 158 and 180 patients with GPA, respectively[2, 3]. Forty-eight patients with meningeal involvement in GPA were disclosed in another case report revision[5]. In a recent French retrospective study, 35 patients had CNS GPA involvement: pachymeningitis was present on 16 and cerebral granulomas in one patient[14].

The pathogenesis of granuloma is not clear and different cells types are involved in the granulomatous lesion[15]. In our patient we believe that may have occurred a combination of major mechanisms: a granulomatous invasion by contiguous extension from the nasal/paranasal sinuses and/or orbital granuloma into the meninges, or brain; and granulomatous lesions within brain parenchyma.

Evidence suggests rituximab (anti-CD20 agent) is an effective treatment for manifestations such as pulmonary vasculitis and glomerulonephritis[16]. It is not inferior to daily CYC in inducing remission in GPA ANCA-positive patients and it could be superior in re-

TABLE I. CLINICAL CHARACTERISTICS AND OUTCOMES IN PREVIOUS CASES OF GPA WITH NEUROLOGICAL INVOLVEMENT TREATED WITH RITUXIMAB

Reference	Patient (years)	Neurologic manifestation	Previous therapy	Treatment protocol	Follow-up (months)	Time to relapse	RTX cycles	Outcome
Bawa et al. 2007[22]	Female, 36y	Meningitis, papilledema and a XIIth nerve palsy	CYC pulse and GC pulse	1st day: rituximab (1gr iv) methylprednisolone (250mg iv); 2nd day: CYC 750mg > repeated once 2 weeks later	6	No relapse	1	Complete clinical remission, MRI findings persistent
Tamura et al. 2007[23]	Female, 19y	Retroorbital granuloma and hypertrophic pachymeningitis	CYC pulse, GC oral, and MTX	Rituximab (375mg/m2) weekly in four weeks	12	9	2	BVAS (19 to 2)
Tamura et al. 2007[23]	Female, 35y	Retroorbital granuloma and hypertrophic pachymeningitis	GC oral and pulse, and MTX/CSA	Rituximab (375mg/m2) weekly in four weeks	5	No relapse	1	BVAS (13 to 3)
Sharma et al. 2010[24]	Female, 22y	Nodular scleritis, Pachymeningitis, cranial nerve palsies	GC oral and pulse, MTX, and CYC pulse	Rituximab (375mg/m2) weekly in four weeks	6	6	2	Clinical remission MRI not described
Just et al., 2011[25]	Female, 28y	Pachymeningitis	CYC oral, GC oral, MTX, and AZA	Rituximab (375mg/m2) weekly in four weeks	30	9	4	Complete clinical and MRI remission
Benucci et al., 2013[26]	Female, 37y	Aseptic meningitis	GC oral, CYC oral and MTX	Rituximab (375mg/m2) monthly in 6 months	30	6	2	Complete remission and partial remission in MRI
Presented case	Male, 50y	Pachymeningitis and cerebral granuloma	CYC oral, GC oral, AZA and MTX	Rituximab (375mg/m2) weekly in four weeks	6	–	2	Complete clinical remission and MRI improvement

BVAS: Birmingham vasculitis activity score modified for GPA; CYC: cyclophosphamide; MTX: methotrexate; CSA: cyclosporine A; RTX: rituximab; AZA: azathioprine; IV: intravenous

lapsing disease[17]. Rituximab is also effective in preventing relapse and has proven to be superior to azathioprine in maintaining remission[18].

However, it is still unclear whether rituximab is effective in the treatment of necrotizing granulomata in a diversity of locations[12]. A controlled trial has shown the lack of efficiency of rituximab in eight patients with refractory granulamatous GPA. One patient with lung involment, two with subglottic stenosis, and five with retro-orbital granulomata[12].

In an uncontrolled retrospective study that included 59 patients receiving rituximab for refractory GPA, a good overall efficacy was reported, with 61.3% of patients achieving complete remission or significant improvement. Granulomatous manifestations, such as orbital granuloma and pachymeningitis, were more refractory to rituximab than vasculitic manifestations. One patient achieved complete remission and five (41.7%) improved, of a total of 12 with GPA and pachymeningitis treated with rituximab[19].

Indeed, it has been postulated that refractory granulomatous disease is particularly difficult to treat and may be pathogenically different from the majority of patients with GPA with predominantly vasculitic manifestations. It may be speculated that a different inflammatory environment within these lesions, responsible for sustained granuloma formation and fibrosis, may justify a relative resistance towards immunosuppressive agents, including rituximab[12, 19].

In this patient, the cerebral granulomas did not disappear completely but were significantly reduced six months after rituximab treatment. This may indicate post-inflammatory fibrosis, which is commonly observed in retro-orbital lesions[20].

Series reporting the use of rituximab in the treatment of neurologic manifestations in GPA are presented in Table I. Successful treatment of pachymeningitis has been reported in these cases[21-25]. We highlight that these results have to be cautiously interpreted, namely because of different glucocorticoid and CYC regimens before rituximab administration. Additionally, diverse rituximab regimens and different intervals between cycles require validation in a larger cohort.

Several questions regarding rituximab use in GPA remain unanswered: what should be the maintenance strategy after rituximab induction? When should these patients be re-treated with rituximab? Some indicators have been proposed[4,19]: at time of clinical and/or radiological relapse, guided by B-cell return or ANCA titters, or routine with a fixed interval. In our case, given the severity of manifestations and azathioprine intolerance, we decided to retreat at six months despite the lack of clinical or radiological signs of relapse.

In conclusion, GPA-associated granulomatous lesions of the CNS impose the need for a diagnostic work-up and treatment in order to prevent or reduce potential damage. Our case highlights that rituximab may be a good treatment option for meningeal involvement and cerebral granulomas in GPA patients.

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