Case Report

Wegener’s Granulomatosis Presenting with Pachymeningitis: Clinical and Imaging Remission by Rituximab

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1. Introduction

Pachymeningitis is a rare feature of Wegener’s granulomatosis (WG) and an uncommon initial manifestation of the disease [1]. We demonstrate that pachymeningeal lesions refractory to conventional therapy can resolve completely by the addition of Rituximab (RTX) to standard remedies. This case also illustrates that besides global headache, WG-related pachymeningitis may occasionally manifest itself by lateralized pain and cranial nerve involvement [2–5].

2. Case Report

In 2004, a 27-year-old Caucasian female was admitted for persistent right-sided ear, jaw, and neck pain, with recent advent of tinnitus, hearing loss, and nasal sores. A CT-scan showed mucosal thickening of the maxillary sinuses without bony erosions. A biopsy from nasal mucosa showed vasculitis and granuloma formation. Chest CT showed an apical infiltrate in the right lung and no mediastinal lymphadenopathy. A transthoracic lung biopsy revealed necrotic tissue and chronic inflammation with granuloma formation. Bronchoalveolar lavage (BAL) fluid was negative for bacterial growth, mycobacterial PCR, and malignant cells. A PPD skin test was negative. However, the patient tested positive for PR-3 ANCA (49 U/mL, <10). Blood cell counts were normal, CRP below 15 mg/L, creatinine clearance, and urinalysis were normal. Based on these findings, the patient was diagnosed with Wegener’s granulomatosis [6].

A cerebral MRI showed meningo-dural enhancement, and additional diagnostic workup revealed a right pulmonary infiltrate and positive PR-3 ANCA. Biopsies from nasal mucosa and lung showed chronic inflammation with granuloma formation. Based on these findings the patient was diagnosed with Wegener’s granulomatosis with pachymeningitis. There was no clinical response to oral Prednisolone and Cyclophosphamide, but complete clinical and imaging remission was achieved by adding Rituximab.

Cerebral magnetic resonance imaging (MRI) with gadolinium showed infratentorial, meningeal thickening along the right cerebellar tentorium, the cerebellopontine angle ascending into the right foramen jugulare. Besides, a thrombus extending from the right sinus transversus to bulbous vein jugularis was diagnosed. No nodular enhancement or infarcts were noted. Based on these findings, Wegener related pachymeningitis was suspected although not histologically confirmed.

Induction treatment included intravenous methylprednisolone pulses (1 gram/day for 3 days), plasma exchange on 5 consecutive days, and oral Cyclophosphamide. Low molecular weight heparin and warfarin were added for prophylaxis against progression of cerebral venous thrombosis.
Table 1: Clinical characteristics and outcomes in previous cases of Wegener’s meningitis treated with Rituximab.

| Reference          | Patient   | Previous therapy | Treatment protocol | Followup (mo) | Time to relapse (mo) | Rituximab cycles | Outcome                        |
|--------------------|-----------|------------------|--------------------|---------------|----------------------|-------------------|--------------------------------|
| Bawa et al. 2007   | Female    | CYC pulse and GC pulse | First day: Rituximab (1 g. iv.) Methylprednisolone (250 mg iv.) | Second day: Cyclophosphamide (750 mg iv.) Regime repeated once 2 weeks later. | 6         | No relapse 1 | Complete clinical remission, MRI findings persistent. |
| Tamura et al. 2007 | Female    | CYC pulse, GC oral, and MTX | Rituximab (375 mg/m²) weekly in four weeks | Prednisolone 100 mg/day gradually tapered | 12       | 9      | 2 | BVAS (19 → 2) |
| Tamura et al. 2007 | Female    | CYC pulse, GC oral and pulse, and MTX/CSA | Rituximab (375 mg/m²) weekly in four weeks | Prednisolone 50 mg/day gradually tapered | 5         | No relapse 1 | BVAS (13 → 3) |
| Henes et al. 2007  | Male      | CYC oral and pulse, GC oral, and INF MTX/CSA | Rituximab (375 mg/m²) weekly in four weeks | Prednisolone 1 mg/kg/day gradually tapered. Leflunomide 20 mg/day | 21       | 18     | 2 | Some clinical and MRI improvement. |
| Sharma et al. 2010 | Female    | GC oral and pulse, MTX, and CYC pulse | Rituximab (375 mg/m²) weekly in four weeks | Prednisolone 60 mg/day gradually tapered. | 6         | 6      | 2 | Clinical remission MRI not described |
| Presented case     | Female    | CYC oral and pulse, GC oral, MTX, and AZA | Rituximab (375 mg/m²) weekly in four weeks | On separate day in each week: Methylprednisolone (250 mg iv.) Cyclophosphamide (500 mg/m² iv.) | 30       | 9      | 4 | Complete clinical and MRI remission |

BVAS: Birmingham vasculitis activity score modified for WG, CYC: Cyclophosphamide, GC: Glucocorticosteroids, MTX: Methotrexate, CSA: Cyclosporine A, INF: Infliximab, AZA: Azathioprine. iv.: intravenous.

Figure 1: (a) T1W gadolinium-enhanced MRI 12.20.2006 showing meningeal thickening with enhancement on the dorsal and lateral aspects of the clivus close to the transverse sinus (arrows). (b) T1W gadolinium-enhanced MRI 06.08.2007. The meningeal thickening on the back of clivus has completely regressed, but the thickening on the right side near the transverse sinus remains visible. (c) T1W gadolinium-enhanced MRI 02.12.2009. Meningeal thickening and enhancement have resolved completely.

However, the Cyclophosphamide dosing target at 2 mg/kg could not be achieved due to debilitating nausea and liver toxicity, and she suffered from persistent cervicocranial pain despite normal CRP, PR-3 ANCA seroconversion, and partial regression of meningeal pathology by MRI.

In December 2006, the patient complained of diplopia. A repeat MRI scan showed marked progression of the infratentorial dura-meningeal enhancement (Figure 1(a)), whereas partial revascularisation of the transverse sinus was noted. Azathioprine 50 mg/daily was added to the current Prednisolone medication (50 mg daily), but it had
to be discontinued after 3 weeks due to intolerable nausea and elevated liver enzymes. Due to similar drug toxicity, Methotrexate 15 mg weekly added to daily 40 mg Prednisolone medication was abandoned after 2 months treatment. In February 2007, Rituximab was added as follows: 4 weekly Rituximab infusions (375 mg/m²) combined with i.v. Methylprednisolone (250 mg) and i.v. Cyclophosphamide (500 mg/m²) on a separate day. Already within 1 week after the first infusion, diplopia and neck pain had vanished. A follow-up MRI at 6 months showed partial regression of the meningeal pathology (Figure 1(b)), and chest CT revealed complete regression of the lung infiltrate. PR-3 ANCA remained negative. Cyclophosphamide was discontinued and Prednisolone gradually tapered to 5 mg daily. Subsequently, relapsing neck and ear pain with concomitant epistaxis, nasal sores or sinusitis occurring at 8–10 months intervals have been successfully brought into remission 4 times using the treatment protocol described above. PR-3 ANCA has been undetectable throughout.

An MRI-scan in February 2009 showed complete regression of meningo-dural enhancement (Figure 1(c)).

**3. Discussion**

Global headache is the most frequent manifestation of WG related pachymeningitis although the condition may occasionally manifest itself with lateralized pain and cranial nerve involvement like in the present case [2–5].

Signs and symptoms of meningeal involvement in WG may result from different disease processes including vasculitis, bony destruction by invasive inflammatory cell infiltration or intraparenchymal granuloma formation [3, 5]. Besides, the increased risk of complicating venous thromboembolism reported recently should be considered as illustrated by the sinus thrombosis encountered in this case [11].

The relative contribution of these pathways cannot be settled in this case, but the absence of destruction and granulomatous lesions by MRI favours a dominant role of vasculitis. Although conventional therapy using oral Prednisolone and Cyclophosphamide was followed by regression of the meningeal lesions seen on MRI, a parallel clinical response was not achieved. Probably, this is due to the submaximal dosing of these agents due to adverse effects.

Based on reports on favourable responses of RTX in refractory WG, we decided to add Rituximab to i.v. CYC and Glucocorticoid pulses. Although the exact mechanism behind the response to RTX in WG patients is unknown, it is likely that targeting CD20+ B-cells, which are precursors of ANCA-producing plasma cells, is important as evidenced by the long-term PR-3 ANCA seroconversion observed in this patient.

Successful treatment of Wegener's meningitis has been reported in the past (Table 1) [7–10]. This case is unique by demonstrating that multiple RTX cycles can be administered safely and effectively, resulting in long-term complete clinical and imaging remission despite substantially reduced immunosuppressive comedication, glucocorticoids in particular (Figure 2).

The effect of each single agent applied in the present combination protocol can not be determined. However, as shown in Figure 2, a marked reduction of the median PDN and CYC doses was observed during RTX treatment as compared with the pre-RTX period, thereby supporting the notion of a specific effect of RTX on WG disease pathways. This view is further supported by the need for repeat infusions (Figure 2).

In conclusion, this paper illustrates that WG may present with localized meningeal involvement and that Rituximab added to conventional agents has a steroid sparing effect and can lead to clinical and imaging remission in Wegener-related pachymeningitis.

**Conflict of Interests**

The authors declare that there is no conflict of interests.

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**Figure 2:** Cumulated annual Prednisolone and Cyclophosphamide (CYC) dose (gram). Rituximab (RTX) treatment cycles are indicated by arrows.
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