Successful Treatment with Rituximab for Granulomatosis with Polyangiitis and Multiple Cranial Neuropathies

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Abstract:
We herein report a case of granulomatosis with polyangiitis in a 73-year-old man. He had experienced bilateral ptosis, redness of both eyes, right facial weakness, and hearing loss in the right ear for two months. Myeloperoxidase anti-neutrophil cytoplasmic antibody was positive. Corticosteroids and intravenous cyclophosphamide pulse therapy yielded a response. After the fourth pulse of cyclophosphamide, he developed headache, diplopia, restricted left eye movement, right facial palsy, and hearing loss in the right ear. A one-year remission period was achieved by increasing the steroid and rituximab doses. Rituximab was effective against the relapse of granulomatosis with polyangiitis and cranial neuropathy.

Key words: granulomatosis with polyangiitis, MPO-ANCA, rituximab, cyclophosphamide, cranial neuropathy

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Introduction
Granulomatosis with polyangiitis (GPA) is an autoimmune vasculitis of small- to medium-sized blood vessels. The classic or complete form of GPA affects the upper respiratory tract, lungs, and kidneys. It can also occur in the limited form, which usually involves the head and neck. The Chapel Hill 2012 Consensus Criteria define GPA as “necrotizing granulomatous inflammation usually involving the upper and lower respiratory tract and necrotizing vasculitis affecting predominantly small to medium vessels”(1).

Treatments for GPA involve intensive immunosuppressive therapy with high-dose corticosteroids and cyclophosphamide or rituximab to induce remission. Once remission is achieved, patients are switched to less-toxic maintenance immunosuppression, such as azathioprine and low-dose corticosteroid (2). Localized GPA typically manifests with middle ear and respiratory tract features such as otitis media, sinusitis, nasal collapse, and airway stenosis.

We herein report a case of localized GPA that relapsed, presented with progressive and multiple cranial nerve palsies, and responded to rituximab treatment.

Case Report
The patient was a 73-year-old man with GPA who had no previous medical history. His family history was unremarkable. He had experienced bilateral ptosis, redness of both eyes, right facial palsy, and hearing loss in the right ear for two months. He was referred to our institution because the symptoms continued to progress.

On an examination, he appeared ill, with a pulse rate of 72 beats/min; blood pressure, 124/74 mmHg; respiratory rate, 10 breaths/min; oxygen saturation, 96%; and temperature, 37.0°C. His height was 157 cm, weight 50 kg. His eyes were congested, and he had pain in both eyes and face. Saddle nose deformity was not observed. Breathing sounds were clear on chest auscultation. Body edema was not observed. On a neurological examination, he was alert and showed bilateral hypoaesthesia, a decreased light reflex in the right eye, bilateral ptosis, right eye abduction limitation, diplopia (right lateral gaze), reduced superficial sensation at the upper right part of the face, right facial muscle weakness, dysgeusia, and mild bilateral hearing loss.

Initial laboratory studies showed the following: a white blood cell count of 6,200/mm³ (neutrophils 79.8%, lymphocytes 14.8%, monocytes 4.7%, eosinophils 0.5%, and baso-
Chest radiographs and computed tomography (CT) images were normal. Brain magnetic resonance imaging (MRI) revealed dural thickening in both temporal lesions, but the trigeminal, facial, and auditory nerves showed no gadolinium enhancement. In the paranasal sinuses, mucosal thickening of the maxillary sinuses, minimal fluid retention, and bone wall thickening were detected, indicating chronic sinusitis. Inflammation of the bilateral ocular conjunctiva was also observed. Overall, the findings were indicative of right-dominant bilateral otitis media.

Cryptococcus neoformans antigens and aspergillus antigens were both negative. Anti-Sjögren’s syndrome (SS)-A, SS-B, ribonucleoprotein, double-stranded DNA immunoglobulin G, and cyclic citrullinated peptide antibodies were not detected. A urinalysis showed no urine protein or occult blood. In the cerebrospinal fluid (CSF) test, the lumbar CSF opening pressure was 130 mmH₂O, number of cells was 20/μL (lymphocytes, 20, neutrophils, 0), protein level was 80.8 mg/dL, glucose level was 59 mg/dL, β-D-glucan <6 pg/mL, C-reactive protein (CRP) 6.22 mg/dL, aspartate aminotransferase 12 IU/L, alanine aminotransferase 12 IU/L, blood urea nitrogen 12.5 mg/dL, creatinine 0.55 mg/dL, sodium 140 mEq/L, potassium 4.3 mEq/L, and chloride 102 mEq/L, glucose, 99 mg/dL, HbA1c, 6.1%; IgG, 926 mg/dL, prothrombin time 11.2 seconds, international normalized ratio (INR), 0.9 (normal range <1.15), activated partial thromboplastin time 28.7 seconds (normal range <42 s), rheumatoid factor 10 IU/mL (normal range <15 IU/mL), proteinase3 anti-neutrophil cytoplasmic antibody (PR3-ANCA) <1.0 U/mL (normal value <3.5 U/mL), myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA) 4.8 U/mL (normal range <3.5 U/mL), angiotensin-converting enzyme 8.1 U/L (normal range 8.3-21.4 U/L), soluble interleukin-2 receptor 496 U/mL, and IgG index was 2.08, and myelin basic protein level was <40 mg/dL. An oligoclonal band was not detected.
a biopsy of the thickened nasal mucosa. At the biopsy site of the sinus mucosa, numerous eosinophils, neutrophils, and plasma cells were found in addition to capillaries with thickened basement membranes and vasculogenesis. We observed no evidence of fibrinoid necrosis, other vasculitis, or vascular inflammation that would clearly indicate vasculitis. In addition, no fungal infection or malignancy was found.

Based on the otitis media, scleritis, hypertrophic pachymeningitis, and PR3-ANCA-positive findings, the patient was diagnosed with localized GPA (MPO-ANCA-positive). Furthermore, according to the algorithm of the European Medicines Agency, this case is confirmed by the GPA for the diagnosis of ANCA-related vasculitis (3).

The patient was started on treatment with 2 courses of intravenous pulses of methylprednisolone 1,000 mg/day for 3 days, which resulted in rapid improvement of bilateral ptosis, right eye abduction limitation, diplopia, reduced superficial sensation in the upper right side of the face, dysgeusia, and bilateral hearing loss. CRP and MPO-ANCA became negative. However, the bilateral hypoplasia, decreased right-eye light reflex, and facial muscle weakness on his right side remained. His oral prednisolone dose was 50 mg/day after intravenous methylprednisolone (IVMP) 1,000 mg/day for 3 days, and he received 4 doses of intravenous cyclophosphamide 500 mg (10 mg/kg) at monthly intervals. The dose of prednisolone was gradually tapered to 15 mg/day.

Four weeks after the fourth pulse of cyclophosphamide, he developed a headache, diplopia, restricted left-eye movement in all directions, weakness of the right facial muscles, and exacerbation of hearing loss in the right ear. No symptoms other than cranial nerve issues and headache were observed. The levels of MPO-ANCA (2.8 U/mL) and CRP (3.52 mg/dL) were increased, and PR3-ANCA was absent. Gadolinium-enhanced brain MRI detected no evidence of cerebral thickening. However, it did reveal persistent mucosal thickening of the sinus and pachymeningitis despite improvement in the symptoms of sinusitis and otitis media. We therefore diagnosed the patient with localized GPA relapse and reinitiated methylprednisolone at 1,000 mg/day for 3 days.

Prednisolone was increased to 50 mg/day, and rituximab was started because intravenous cyclophosphamide monthly was not sufficiently effective. Rituximab was administered at 375 mg/m² weekly for a total of 4 doses. His headache soon improved. Diplopia, eye movement restriction, right facial muscle weakness, and right hearing loss gradually improved. No side effects of rituximab were observed. The patient was switched to maintenance therapy with azathioprine for 6 months after completing the rituximab course, and the prednisolone dose was slowly tapered to 5 mg/day. He remained in good clinical condition except for mild residual weakness of the right facial muscles for one year following the completion of rituximab.
GPA (13). Furthermore, seronegative GPA presenting with multiple cranial nerve palsies was reported (14). Although MPO-ANCA was positive in our case, we diagnosed it as GPA based on the clinical symptoms and pathological findings.

According to a previous study on refractory GPA, rituximab therapy resulted in complete remission/improvement in 89.2% of patients with renal disease and 80.8% with alveolar hemorrhaging. However, for orbital mass and pachymeningitis cases, rituximab therapy resulted in improvement in only 44.4% and 49.9% of patients, respectively (15), suggesting that rituximab may be more effective for treating vasculitis than for granulomatous manifestations. Furthermore, orbital pseudotumor and pachymeningitis may cause scarring instead of ongoing inflammation; meanwhile, rituximab was effective in cranial neuropathies caused by granuloma lesions (16). Regarding the effects of rituximab on ANCA-associated vasculitis, most studies have reported >80% complete or partial remission rates, with the lowest response (37.5%) obtained for granulomatous lesions (17). In the current case, hypertrophic pachymeningitis at the site of multiple cranial neuropathies did not lead to progressive scarring due to long-term inflammation. We believe that rituximab might have been effective if it had been administered before irreversible scarring changes occurred.

The RAVE and RITUXIVAS studies both showed the non-inferiority of rituximab compared to cyclophosphamide in AAV (18, 19). However, the results from these trials cannot necessarily be applied to our patient. The RITUXIVAS trial and RAVE studies did not have any patients with cranial nerve palsies in the rituximab treatment arm. Nevertheless, case series suggest that rituximab can be effective against cranial neuropathy of GPA (7, 20). From 1985 to 2003, 23% of 350 patients with ANCA-associated vasculitis exhibited treatment resistance. A low glomerular filtration rate, female sex, MPO-ANCA positivity, older age, and chronic kidney biopsy histology have been shown to be risk factors for treatment resistance (21). The present case met the following two criteria: positive for MPO-ANCA and older age. Although IVMP was effective, we reduced the amount of prednisolone taken to 15 mg/day at 4 months after treatment initiation to avoid infections. Combining high-dose steroids and cyclophosphamide had a high probability of resulting in concomitant infections; thus, the prednisolone dose was reduced. Relapse occurred because the standard dose of intravenous cyclophosphamide (IVCY) was reduced from 15 mg/kg to 10 mg/kg every 4 weeks. When recurrence occurred, we could have responded by increasing the dose of prednisolone and IVCY, but the patient was relatively old (73 years old), so we stopped IVCY administration and initiated rituximab therapy to prevent side effects such as infections.

Regarding rituximab therapy, 3 of 28 responders (11%) followed for at least 12 months had relapsed by that time point. A further 16 had to repeat rituximab treatment due to an incomplete response or early symptoms suggestive of relapse but without sufficient disease activity. All patients responded after repeated rituximab treatment, which was evidenced by no further relapses and a decreased dose of glucocorticoids. At 18 months of follow-up, a further 2 patients had suffered disease relapse (2/17, 12%) (7). As demonstrated by several clinical trials, induction remission therapy with rituximab, in which prednisolone was administered for 14 weeks, resulted in favorable outcomes, with 48% of the patients maintaining remission at 12 months and 36% maintaining it at 18 months (22). In addition, maintenance remission therapy with rituximab once every 6 months has been shown to lead to a positive response (23).

Rituximab is commonly administered at 375 mg/m² once a week for 4 weeks; however, in few cases, rituximab administration at 375 mg/m² once only and initial prednisolone at 20 mg/day successfully induced remission and maintained patient safety (24). In the present case, rituximab rapidly improved the symptoms during relapse. In elderly patients, adjusting the number of rituximab doses and concomitant prednisolone doses over the course of the treatment may reduce the risk of infection. The remission rates for rituximab and cyclophosphamide for vasculitis are similar, but some patients are contraindicated for cyclophosphamide therapy or refuse such therapy because of concerns about myelosuppression, fertility, hair loss, and malignancy risk. Furthermore, the use of high-dose steroids is challenging for people with severe diabetes and osteoporosis. High-dose steroids and cyclophosphamide induction can be avoided by considering the first-line induction of rituximab and low-dose steroids during remission or maintenance.

**Conclusion**

We herein report a case of local GPA presenting mainly with cranial neuropathy symptoms. Rituximab treatment was effective in relieving the cranial neuropathy induced by GPA when relapse occurred with cyclophosphamide or corticosteroid treatment.

**The authors state that they have no Conflict of Interest (COI).**

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