

Granulomatosis and Polyangiitis: the Rituximab Option

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Granulomatosis and polyangiitis (formerly known as Wegener’s granulomatosis) is a multiorgan disease of unknown etiology characterized by granulomatous inflammation and vasculitis of small- and medium-sized blood vessels [1]. The intensity of treatment is dictated by the severity and extent of the condition [1]. A severe disease course may threaten the function of vital organs as well as the patient’s life. The standard of care of severe GPA includes an induction phase with cyclophosphamide combined with high doses of glucocorticoids [1], followed by maintenance therapy with either methotrexate or azathioprine [1], while limited disease may be controlled with methotrexate or azathioprine [1]. During the past decade, the field of rheumatology has been revolutionized by the use of biologic agents, including successful reports on the effect of rituximab in anti-neutrophil cytoplasmic antibody-related vasculitis [1,2]. The rationale for using this agent is based on its ability to deplete B cells, which are important players in the pathogenesis of GPA [1]. We present two cases of GPA successfully treated with rituximab.

PATIENT DESCRIPTIONS

CASE 1

A 30 year old otherwise healthy woman presented to her family physician with complaints of runny nose and dry cough.

Over the subsequent month, she developed swollen and painful knees and left ankle, a rash over her legs, and red eyes. She denied fever, chills, headache, past sinusitis, chest pain, dyspnea, abdominal pain or diarrhea. Her physical examination disclosed signs of synovitis in her knees and left ankle, palpable purpura over her legs and scleral erythema suggestive of episcleritis. The blood tests showed mild normocytic anemia (hemoglobin 11.4 g/dl, mean corpuscular volume 81), leukocytosis with neutrophilia, elevated acute-phase reactants (erythrocyte sedimentation rate 56 mm/hr, C-reactive protein 11.7 mg/L), mildly increased rheumatoid factor (33 IU/ml) and C4 (46.8 g/L), a C-ANCA titer of 1:160 with positive anti-proteinase3 (157 IU/ml), as well as proteinuria (717 mg/day) and red blood cells in the urinary sediment. A sinus computed tomography scan demonstrated mild opacification in her maxillary sinus, and a chest CT scan showed a lesion in her right lower lobe with irregular borders, suggestive for a granuloma. At this stage, she was referred to our unit and started on prednisone (40 mg/day) which led to amelioration of her symptoms and improved laboratory findings. Her proteinuria, however, rose to 1300 mg/day. A kidney biopsy demonstrated pauci-immune crescentic glomerulonephritis. The combination of upper respiratory symptoms, suspected lung granuloma, pauci-immune crescentic glomerulonephritis, oligoarthritis, vasculitic rash and episcleritis in the presence of C-ANCA and anti-proteinase3 was typical of GPA. She was subsequently treated with intravenous cyclophosphamide according to the Cyclops protocol[®] [1] and high doses of prednisone, with

prompt improvement in her condition. However, after the sixth infusion of cyclophosphamide, with prednisone having been tapered down to one-half of the initial dose, the episcleritis recurred, followed by polyarthritis, purpural rash and proteinuria. At this point, she was treated with rituximab (1 g twice a day) and glucocorticoids. A few weeks later, all her symptoms had completely resolved and the laboratory findings were normal. At her last visit, 2 years after the initial presentation, the patient is asymptomatic on continued maintenance therapy with methotrexate and rituximab only.

CASE 2

A 60 year old woman presented to our unit with auricular chondritis, migratory arthritis, myalgia, recurrent episodes of vasculitic rash in the presence of C-ANCA at a titer of 1:320, and a positive test for anti-myeloperoxidase. She was diagnosed as having relapsing poly-chondritis with AAV. Over the years, she was treated with methotrexate and, for a short period, with azathioprine.

In 2009, she presented with pain and proptosis in her left eye. She denied fever, chills, weight loss, night sweats, past sinusitis, palpitations, diarrhea, respiratory complaints or chest pain. Her physical examination disclosed proptosis in her left eye without any other significant sign. Laboratory tests were significant for normocytic anemia, elevated acute-phase reactants (ESR 84 mm/hr, CRP 1.2), a C-ANCA titer of 1:320 and positive anti-myeloperoxidase (79 IU/ml). A CT scan showed a left enhanced intraorbital lesion

AAV = anti-neutrophil cytoplasmic antibody-related vasculitis
 ESR = erythrocyte sedimentation rate
 CRP = C-reactive protein

GPA = granulomatosis and polyangiitis

C-ANCA = anti-neutrophil cytoplasmic antibody

Left orbital pseudotumor (arrow) in a patient with granulomatosis and polyangiitis



that involved the left lateral rectus muscle and the lacrimal gland. In addition, this lesion reached the optic nerve [Figure]. A biopsy of the lesion showed evidence of necrotizing vasculitis. The combination of vasculitic orbital pseudotumor associated with anti-myeloperoxidase led to the diagnosis of GPA. Initially, she was treated with methotrexate and glucocorticoids, but her condition did not improve. Moreover, a follow-up CT scan showed a mild progression of the retro-orbital lesion. The patient's symptoms and signs resolved following treatment with rituximab (1 g twice a day) and glucocorticoids. No progression has been noted on follow-up CT scans.

COMMENT

We describe two cases of GPA with different manifestations. Each demonstrated a similar dramatic and rapid clinical response to rituximab and glucocorticoids after failure of the conventional first-line treatment.

Over the last decade, the beneficial effect of rituximab had been reported in several case reports or non-controlled studies [1,2]. Avshovich et al. reported the case of a 50 year old man with GPA involving the sinus, lung and later the orbits with bilateral orbital pseudotumor. This patient was initially treated with different drug regimens including glucocorticoids, cyclophosphamide, methotrexate and azathioprine but eventually required treatment with rituximab (in addition to concurrent treatment with glucocorticoids and cyclophosphamide), resulting in the complete resolution of his symptoms [1]. Recently, two well-controlled studies on the effects of rituximab in AAV appeared in the literature [3,4]. The first was a non-inferiority study (RAVE) that compared rituximab to cyclophosphamide and showed that treatment with rituximab and glucocorticoids was not inferior to the standard regimen of cyclophosphamide with glucocorticoids in its ability to induce complete remission by 6 months in recent-onset severe AAV (mostly GPA patients) [3]. That study also found rituximab to be superior in a subgroup of patients suffering from relapsing disease. The second trial (RITUXVAS) compared the same therapeutic options in AAV with renal involvement [4], and the conclusions were similar to those of the RAVE study.

Orbital pseudotumor, which responded to treatment with rituximab, was a prominent symptom in our second case presentation. While cyclophosphamide does not seem to be effective in cases of retro-orbital tumors due to GPA [2], a cohort study that examined the efficacy of rituximab in GPA with refractory manifestations in the head and neck reported a satisfactory response to rituximab [5]. Overall, 32 of 34 patients derived considerable benefit from the treatment with rituximab, enabling discontinuation of other immunosuppressive drugs and tapering down of the glucocorticoid dosage. In addition, four of

five patients with orbital pseudotumor had a good response to rituximab [5].

In conclusion, we describe two patients with severe and life-threatening manifestations of GPA who responded dramatically to rituximab. For decades, the sole treatment option for GPA had been cyclophosphamide with glucocorticoids. Our findings together with those of other publications strengthen the position of rituximab as an alternative therapeutic option for patients with severe GPA in new-onset as well as in refractory/relapsing disease when conventional immunosuppressive treatment has failed. However, several important questions concerning the use of rituximab in terms of safety, as well as its long-term effects still remain unanswered, and further investigations are warranted.

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“Wars damage the civilian society as much as they damage the enemy. Soldiers never get over it”

Paul Fussell (1924-2012), American cultural and literary historian, best known for his writings about World War I and II, which explore what he felt was the gap between the romantic myth and reality of war