CASE REPORT

Successful treatment using rituximab in a patient with refractory polymyositis complicated by scleroderma renal crisis

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SUMMARY

Corticosteroids are the first-line treatment for patients with inflammatory myopathies. Myositis can be a clinical feature of scleroderma (polymyositis–scleroderma overlap syndrome), and treatment of this syndrome is a challenge for clinicians because moderate to high doses of corticosteroids are considered a risk factor for development of acute kidney injury in affected patients. We report here the case of a 56-year-old woman with scleroderma who developed polymyositis and was successfully treated with rituximab. Initial treatment of the polymyositis with prednisolone 40 mg/day was rapidly tapered to 2.5 mg/day due to development of scleroderma renal crisis, for which four weekly infusions of rituximab (500 mg; off-label) were given. She responded well to rituximab in addition to prednisolone 2.5 mg/day. Rituximab may improve inflammatory myopathies, even in cases where high-dose corticosteroids should be avoided due to complications. Rituximab should be considered as a treatment option in cases of refractory polymyositis.

BACKGROUND

Idiopathic inflammatory myopathies, such as polymyositis and dermatomyositis, are a heterogeneous group of chronic disorders characterised by muscle inflammation and proximal muscle weakness. Moderate to high doses of corticosteroids are the standard first-line treatment, either alone or in combination with immunosuppressive agents.¹ Scleroderma, or systemic sclerosis, is a chronic disease that affects connective tissues. Patients with scleroderma may develop inflammatory myopathy, which is called polymyositis–scleroderma overlap syndrome.² Treatment of this syndrome is a challenge for clinicians because moderate to high doses of corticosteroids are considered a risk factor for development of acute kidney injury in patients with scleroderma, leading to a condition known as scleroderma renal crisis.³

We present here a case of polymyositis–scleroderma overlap syndrome. The patient was initially treated with prednisolone 40 mg/day for polymyositis, but the dose had to be rapidly tapered down to 2.5 mg/day due to development of scleroderma renal crisis. The myositis then responded well when the anti-CD20 antibody rituximab was given in combination with low-dose prednisolone (2.5 mg/day). Muscle strength also improved without relapse of renal crisis.

CASE PRESENTATION

A 56-year-old Japanese woman, in whom systemic sclerosis (limited cutaneous type) had been diagnosed 6 months previously, was referred to our clinic in June 2015 with worsening malaise and muscle weakness. She had received an angiotensin-converting enzyme (ACE) inhibitor (enalapril) for hypertension. On physical examination, she had pronounced symmetric muscle weakness in the trunk and proximal limbs, and found it difficult to remain sitting upright. She did not complain of dysphagia or shortness of breath. The chest and abdomen were clinically normal. She had sclerosis of the skin restricted to the distal forearms, Raynaud's symptoms and pitting scars on the fingertips, but no calcinosis. She had a body weight of 43.5 kg, a body temperature of 37.0°C, blood pressure of 108/77 mm Hg and a pulse of 111 beats/min.

INVESTIGATIONS

Laboratory investigations revealed a leucocyte count of $4.7 \times 10^9/L$, haemoglobin of 9.3 g/dL, a platelet count of $152 \times 10^9/L$ and a serum C-reactive protein level of 1.5 mg/L. Serum creatine kinase and lactate dehydrogenase levels were mildly elevated at 360 IU/L and 327 IU/L, respectively. Serum creatinine was 0.99 mg/dL. Immunological investigations indicated an antinuclear antibody level of 1:80 (speckled pattern; normal, <1:40). Antibody tests for anti-SS-A, anti-SS-B and anti-RNA polymerase III were positive. Anti-dsDNA, anti-Smith, anti-RNP, anti-topoisomerase I, anti-centromere and anti-aminoacyl-tRNA synthetase antibodies were all negative. Serum complement (C3 and C4) concentrations were normal. Urinalysis was negative for proteinuria and occult blood. A chest radiograph was normal. An electromyogram revealed a myogenic pattern in the iliopsoas, vastus lateralis and paraspinal muscles. MRI showed generalised oedema in the internal obturator, iliopsoas and paraspinal muscles (figure 1A). The patient declined a muscle biopsy. The clinical diagnosis was polymyositis overlap with scleroderma.

DIFFERENTIAL DIAGNOSIS

We could not identify any other cause for this patient's proximal muscle weakness, such as a side effect of medication, an endocrine disease or malignancy. Involvement of the paraspinal muscles, which

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Figure 1 Magnetic resonance imaging-short-tau inversion recovery of the pelvis before (A) and 2 years after (B) the initial treatment with rituximab. Diffuse oedema of the bilateral spinal erector muscles (arrow) seen before treatment shows some resolution after treatment.

is revealed by electromyography or MRI, has been reported in a number of patients with polymyositis.⁴

TREATMENT

She was initially treated with oral prednisolone at a low dose of 10 mg/day, methotrexate and intravenous immunoglobulin (Ig). These treatments did not improve her myositis symptoms, and muscle weakness worsened to difficulty sitting up in bed. One month later, after explaining the risk of acute renal failure as a potential complication, the dose of prednisolone was increased from 10 to 40 mg/day. However, 2 weeks after this increase, she developed acute kidney injury. Blood pressure was 107/68 mm Hg. Blood tests demonstrated a leucocyte count of $3.7 \times 10^9/L$, a haemoglobin of 6.5 g/dL, and a platelet count of $41 \times 10^9/L$ with schistocytes and helmet cells on blood film. Haptoglobin was undetectable. Urinalysis showed 1+ haematuria and negative proteinuria with no casts. Serum creatinine was elevated to 6.21 mg/dL, necessitating haemodialysis. Although a renal biopsy was not performed because of the haemorrhagic risk linked to thrombocytopenia, the clinical and laboratory features suggested scleroderma renal crisis with thrombotic microangiopathy. The dose of prednisolone was rapidly tapered to 2.5 mg/day.

Off-label use of rituximab for immunotherapy was considered and written informed consent was obtained from the patient. Treatment with rituximab according to the regimen used in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis

(four weekly infusions of rituximab at a dose of 500 mg, total 2 g)^{5 6} was initiated. Intravenous Ig was coadministered with the first infusion of rituximab, and low-dose prednisolone (2.5 mg/day) was continued orally.

OUTCOME AND FOLLOW-UP

Treatment with rituximab was effective, muscle strength gradually improved and the creatine kinase level normalised 3 months later. On the basis of a study of maintenance immunosuppressive therapy in ANCA-associated vasculitis,⁷ we had initially planned to administer courses of rituximab 500 mg at 6-month intervals. Rituximab 500 mg was given 6 months after the first infusion as maintenance therapy. However, because of the occurrence of moderate neutropaenia, which was possibly associated with rituximab,⁸ further administration of rituximab was withheld. Two years after the first infusion of rituximab, the patient is receiving only oral prednisolone 2.5 mg/day. Muscle inflammatory oedema observed on MRI showed complete resolution (figure 1B). The patient is currently in complete clinical and biochemical remission with regard to myositis, although she remains on haemodialysis.

DISCUSSION

Rituximab is an antibody that targets CD20, and treatment with rituximab leads to B-cell depletion in most patients. Since the publication of a randomised trial of rituximab in myositis,⁷ more attention has been paid to the potential of this biologic for treatment of inflammatory myopathies. In that trial, rituximab was administered to patients refractory to at least 1 month of treatment with high-dose prednisolone (1 mg/kg). Patients received two weekly infusions of rituximab at a dose of 1 g (total 2 g). Rituximab was effective in 83% of patients when prednisolone was coadministered at a mean dose of 20.8 mg/day without reduction for 16 weeks.⁹ Our patient could not continue on prednisolone 40 mg/day due to development of scleroderma renal crisis, and the dose was rapidly tapered down to 2.5 mg/day. She responded well to combination treatment with the low-dose prednisolone and rituximab, with visible improvement in muscle strength a few months later.

Scleroderma renal crisis is an infrequent but serious complication of systemic sclerosis. Some of the risk factors for scleroderma renal crisis that have been identified include the diffuse cutaneous type of scleroderma, use of glucocorticoids and the presence of serum anti-RNA polymerase III antibody.^{3 10} Our patient had the limited cutaneous type but was anti-RNA polymerase III antibody-positive. We believe that the increase in dose of prednisolone (from 10 to 40 mg/day) may have precipitated the renal crisis because it occurred 2 weeks after the dose increase. We should have considered rituximab as a treatment option before increasing the corticosteroid dose.

Our patient had already been treated with an ACE inhibitor for hypertension prior to the onset of her renal crisis. Although survival of patients with scleroderma renal crisis has improved dramatically with development of the ACE inhibitors,¹¹ there is no clear evidence that prior use of an ACE inhibitor can prevent a renal crisis. Further, a prospective cohort study suggested a trend of worse outcomes in patients who had previously received an ACE inhibitor.¹² Our patient had normal blood pressure when she developed scleroderma renal crisis, and it may be related to her continuous use of an ACE inhibitor beforehand. It has been reported that scleroderma renal crisis occurs in the absence of hypertension in approximately 10% of patients.¹³

Intravenous Ig was co-administered with the first infusion of rituximab in our patient. Given that initial treatment with intravenous Ig alone was not effective, we surmised that administering intravenous Ig with rituximab could have a potentially positive effect because rituximab had been infused with intravenous Ig to treat inflammatory myopathies in a few previously reported cases.^{14 15} However, the clinical significance of this combined therapy is unclear at this time.

Although our patient responded well to rituximab, some would suggest use of alternative immunosuppressive treatment. Cyclophosphamide may be useful in treating myositis.¹⁶ However, because of its severe side effects, particularly bone marrow suppression, infection and induction of malignancy, we considered that its utility would be limited for patients with myositis who do not have interstitial pneumonia or vasculitis. We did not choose methotrexate because it is contraindicated in patients with severe renal insufficiency. Azathioprine or hydroxychloroquine could be a treatment option in our case, but there is no evidence that either of these drugs is of benefit for myositis in patients receiving low-dose corticosteroids.

Long-term outcomes of inflammatory myopathies after remission of the disease is achieved by rituximab remain to be established. In the above-mentioned trial of rituximab in myositis, treatment was effective by 36 weeks after initial administration in 17 of 161 patients (10.5%) in whom a relapse in myositis was recorded.⁹ Nine of the 17 patients were re-treated with rituximab, with improvement in 8 of these 9 patients. Our patient received rituximab at a fixed dose of 500mg on days 0, 7, 14 and 21, and additionally at 6 months. Two years later, she is in complete clinical remission on 2.5mg/day of prednisolone. Careful and continuous monitoring of her condition is needed to detect relapse of myositis.

The findings in this case indicate that physicians should be cognizant of the potential for moderate to high doses of corticosteroids to induce scleroderma renal crisis. Rituximab administration may improve inflammatory myopathies, even in cases where high-dose corticosteroids should be avoided due to complications. Rituximab should be considered as a treatment option in cases of refractory polymyositis.

Learning points

- Scleroderma renal crisis can occur in polymyositis–scleroderma overlap syndrome and might be triggered by glucocorticoids.
- Rituximab may improve inflammatory myopathies, even when high-dose corticosteroids need to be avoided because of complications.
- Rituximab should be considered as a treatment option in cases of refractory polymyositis.

Contributors KI and YM: involved in conception or design of the work. KI and SK: responsible for acquisition of data. KI, TM and YM: drafted the manuscript or revised. All authors: are responsible for analysis and interpretation of data.

Competing interests KI received scholarship donations from AbbVie, Actelion, Astellas, Bristol-Myers, Chugai, Daiichi-Sankyo, Eisai, Eli Lilly, Japan Blood Products Organization, Mitsubishi-Tanabe, Pfizer, Shionogi, Takeda, Teijin, and UCB. TM received scholarship donations from AbbVie, Actelion, Astellas, Bristol-Myers, Chugai, Daiichi-Sankyo, Eisai, Eli Lilly, Japan Blood Products Organization, Mitsubishi-Tanabe, Pfizer, Shionogi, Takeda, Teijin, and UCB. SK received scholarship donations from AbbVie, Actelion, Astellas, Bristol-Myers, Chugai, Daiichi-Sankyo, Eisai, Eli Lilly, Japan Blood Products Organization, Mitsubishi-Tanabe, Pfizer, Shionogi, Takeda, Teijin, and UCB. YM received scholarship donations from AbbVie, Actelion, Astellas, Bristol-Myers, Chugai, Daiichi-Sankyo, Eisai, Eli Lilly, Japan Blood Products Organization, Mitsubishi-Tanabe, Pfizer, Shionogi, Takeda, Teijin, and UCB.

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