CASE REPORT

Immune-mediated necrotising myopathy associated with antibodies to the signal recognition particle treated with a combination of rituximab and cyclophosphamide

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SUMMARY

A 50-year-old man presented with dysphagia and proximal muscle weakness. He was diagnosed with immune-mediated necrotising myopathy associated with antibodies to the signal recognition particle. After an initial response following treatment with high-dose steroids, intravenous immunoglobulin and methotrexate, there was a relapse of the immune condition. The clinical deterioration occurred less than 2 months after disease onset. The refractoriness of this disease was characterised by an increase of the already severe muscle wasting that led to respiratory failure and progressive dysphagia, regardless of the immunosuppressant treatment. At this time the patient was referred to our department. He was restarted on intravenous pulses of methylprednisolone associated with intravenous cyclophosphamide, but with no effect. After 3 weeks, rituximab was started with a dramatic and progressive improvement. There were no complications associated with rituximab/cyclophosphamide treatment and the disease has been kept in remission, for the last 3 years.

BACKGROUND

Idiopathic inflammatory myopathies (IIMs) constitute a highly heterogeneous group of diseases in which polymyositis (PM), dermatomyositis (DM) and inclusion body myositis are the most common phenotypes. Albeit being rare diseases, IIM is the most common type of acquired chronic myopathy in adults.¹ The mechanisms are not fully understood, and for many years, IIMs have been considered T-cell-mediated diseases.² However, the concomitant role of B cells has been put forward by the presence of myositis-associated autoantibodies (anti-Sjogren's Syndrome A, Sjogren's Syndrome B, U1RNP, U3RNP, PM-Scl and Ku) or myositis-specific autoantibodies (MSA) in approximately 40–90% of patients.^{3–5} The detection of MSA led to a reclassification of IIM, taking into consideration this group of antibodies. The antisynthetase syndrome occurs when the clinical features of IIM are associated with the presence of anti-aminoacyl tRNA synthetase antibodies, which are detected in approximately 20% of all IIMs.^{4,5} The antisignal recognition particle (SRP) antibodies, which occur in 4–6% of all patients with IIM, are associated with severe forms of necrotising myopathy, in the absence of inflammatory infiltrates on biopsy.⁶ A study conducted by Benveniste *et al*,⁷ showed that anti-SRP

antibodies levels correlate with disease activity, suggesting a pathogenic role for these autoantibodies. Recently, anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase antibodies have been associated with a rare statin-induced immune-mediated necrotising myopathy that requires prolonged immunosuppressive therapy.^{8,9}

The treatment of IIM relies essentially on corticosteroids. However, many patients fail to respond and the side effects of corticosteroids are inevitable. Other drugs are often used as corticosteroid-sparing agents, most frequently methotrexate, azathioprine and hydroxychloroquine. For patients refractory to conventional immunosuppressive treatment, the use of mycophenolate mofetil, cyclosporin, tacrolimus and cyclophosphamide (CYC), as well as intravenous immunoglobulin (IVIG), has been reported, but with limited success rates or non-sustained responses. Rituximab (RTX), an anti-B lymphocyte monoclonal antibody directed to CD20 expressing cells, seems to be the most promising treatment option for this condition, although a recent trial failed to meet the primary end points.¹⁰ Nevertheless, RTX was shown to be effective in several individual case reports of patients who were refractory to conventional therapies, even in those with a poorer prognosis such as myositis associated with antisynthetase and anti-SRP antibodies. RTX was initially used for the treatment of B-cell lymphomas and currently it is approved for the treatment of some autoimmune diseases, namely rheumatoid arthritis and antineutrophil cytoplasm antibody-associated vasculitis.¹¹ RTX has also been used in several other systemic autoimmune conditions such as lupus erythematosus,¹² immune thrombocytopenic purpura,¹³ Sjogren's syndrome¹⁴ and Castleman's disease.¹⁵

Despite the increasing knowledge on the treatment of IIM in general, little is known on overall response rates and on the best treatment strategy for patients with the immune-mediated necrotising myopathy associated with anti-SRP antibodies. In fact, information about this condition is still scarce and is based on a few case-reports.

We report a case of a less common anti-SRP antibodies-associated necrotising myopathy, refractory to classic immunosuppressive therapy, which was successfully treated with RTX and CYC, achieving a long-lasting remission.

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CASE PRESENTATION

A 50-year-old man, with no relevant medical history, developed dysphagia and proximal muscle weakness of the limbs, associated with pain of the lower limbs. Laboratory tests showed elevated creatine kinase (CK) levels (14 000 IU/L) and positive anti-SRP antibodies. Other immunological tests were negative and thyroid function was normal. An electromyogram confirmed a primary myopathy. A muscle biopsy showed a necrotising myopathy in the absence of inflammatory infiltrates. The patient had never been on statins and concomitant neoplastic conditions were excluded.

He was treated with steroid intravenous pulses (500 mg) and IVIG (400 mg/kg) for 5 days. An improvement in muscle strength and dysphagia was registered soon after the treatment. The patient continued on steroids (prednisolone 60 mg daily corresponding to 1 mg/kg/day) and methotrexate (15 mg weekly). One month later, during a muscular rehabilitation programme, he started feeling worse, with a relapse of the muscle weakness leading to a significant hypoventilation syndrome, at which point the patient was put on mechanical ventilation. During this period, he was kept on the maintenance therapy described above.

He was then referred to our immune-mediated systemic diseases unit. On admission, the patient had severe proximal muscle weakness, with major wasting of muscular mass, and was confined to bed. He had severe involvement of the respiratory muscles with the need for non-invasive ventilation. He was being fed through a nasogastric tube.

INVESTIGATIONS

In our department, laboratory tests showed an inflammatory anaemia (haemoglobin 8.8 g/dL) and an erythrocyte sedimentation rate (ESR) of 114 mm/h. CK level was low (37 U/L), in association with the severe muscle wasting. The neurophysiological study was repeated and confirmed a severe generalised myopathy with a few signs of acute necrosis and normal neuromuscular transmission.

The immune panel confirmed the presence of anti-SRP antibodies.

TREATMENT

The diagnosis of immune-mediated necrotising myopathy associated with anti-SRP antibodies was confirmed and the patient received a new course of intravenous pulses of steroids (methylprednisolone 1 g) for 5 days and CYC 500 mg every other week. Two weeks after the first infusion, there was a sudden worsening of the respiratory function. Given the poor prognosis and refractoriness of this life-threatening condition, RTX (1+1 g, 2 weeks apart) was added to the ongoing immunosuppressive regimen.

OUTCOME AND FOLLOW-UP

The patient was weaned from respiratory support and the tracheostomy was removed 1 week after the first RTX infusion. There was a significant improvement in proximal muscle strength and the patient gradually started to eat. After the second RTX administration and the third infusion of CYC, the patient was discharged to a physiotherapy unit. Four months later, he achieved complete recovery with normal gait. Prednisolone was gradually tapered down to 5 mg/day. CYC (750 mg) was repeated monthly for 4 months and then discontinued. RTX administration was repeated every 6 months.

At 3-year follow-up, the patient had received a total of six courses (2 g each) of RTX; he is currently only on prednisolone 5 mg/day. The patient has been in clinical remission for all this time, and no other side effects or complications have been reported. Blood tests have shown no signs of myositis (CK) or inflammation (ESR/C reactive protein) and there have been no changes in the immune profile, including the immunoglobulin levels.

DISCUSSION

We present a case of refractory necrotising myositis with positive anti-SRP antibodies. We report an excellent response to RTX and CYC treatment, which might have even been life-saving. RTX, a drug that targets B cells specifically, has been described as potentially effective in IIM, despite the evidence from histopathology studies that show that T lymphocytes are the main cell constituents of the inflammatory infiltrates.¹⁶ More recently, the role of B cells has been highlighted, since they have been recognised as major players being antigen-presenting cells, and in T-cell co-stimulation, as well as natural producers of disease-associated antibodies.¹⁷ Furthermore, new MSAs have recently been discovered,¹⁸ which means that many so-called seronegative patients may actually have disease-defining antibodies (potentially pathogenic) in plasma.

IIMs are rare and therefore clinical trials are very difficult to conduct in this subset of patients. As such, case reports and case series are very important to unveil the effects of potential new treatments such as RTX. The first report of RTX use in refractory DM dates back to 2001.¹⁹ Since 2005, several case reports, case series and pilot studies have suggested the potential benefits of RTX for the treatment of refractory IIM. The total number of IIMs treated with RTX presented in the literature is 121,^{7 20–41} excluding the 200 patients enrolled in a recently published trial.¹⁰ These 121 patients had a disease refractory to an average of 2–3 drugs and yet, 90 (approximately 74%) were successfully treated with RTX, although there were different response criteria in the reports (nevertheless, one must bear in mind that the unsuccessful cases are usually not reported or remain unpublished). Concomitant therapies also varied. With respect to the concomitant use of CYC, many patients had received it before RTX, but only five were treated with RTX and CYC concomitantly (3 with good response and 2 with partial improvement).

Of all the reported cases, only 21 had anti-SRP antibodies and were treated with RTX. Two of them showed good response after standard treatment and plasma exchange.²⁴ Pavy *et al*²⁸ described three successful cases, with two having plasma exchange before the RTX infusions. Another two responded to RTX, although without complete recovery.³⁵ Valiyil *et al*³⁶ described eight cases of refractory anti-SRP antibodies-associated myositis treated with RTX, with good response in six. A study using the results of the AIR registry (autoimmunity and RTX) included two patients with positive anti-SRP antibodies of 30 cases of IIM; one was considered responsive to RTX.⁴⁰ Benveniste *et al* included, in a study designed to correlate anti-SRP antibodies titres with disease activity, four patients treated with different combinations of RTX, prednisone, azathioprine, mycophenolate mofetil, methotrexate, IVIG and plasma exchange. All the four patients improved.⁷ Notably, the three cases without a good response to RTX were particularly serious cases, refractory to multiple treatments.

The largest and most recent study addressing the use of RTX in IIM is the RIM trial (RTX in myositis).¹⁰ Rather than being a drug-efficacy trial, the RIM work is a treatment strategy study that intended to compare two different time-points (8 weeks

apart) to initiate treatment with RTX. In this study, regardless of the time when RTX was started, there was a significant improvement in the clinical features of the disease in 83% of the patients. The population enrolled comprised patients with PM, DM and juvenile DM, with only 25 patients having anti-SRP antibodies, and this particular subset was not analysed as a separate group. Recently, a study on prognosis markers in the RIM trial patients did not find a significant correlation between the presence of autoantibodies other than antisynthetase antibodies and clinical improvement, which was analysed independently of RTX treatment.⁴²

In conclusion, we present a case of a patient with an anti-SRP antibodies-associated inflammatory myopathy, refractory to conventional immunosuppressive therapy and with a particularly serious clinical course. Response to treatment with RTX and CYC was impressive, occurring 3 weeks after starting CYC and 1 week after the first RTX infusion. After the induction therapy with CYC for 4 months, RTX was maintained and the patient achieved a sustained full remission at 6 months, which persisted for more than 3 years. No adverse events occurred. In the absence of other studies on efficacy and safety of the concomitant use of RTX and CYC to treat refractory IIM, this report might be of great value for clinicians dealing with similar cases.

Patient's perspective

In February, 2011, I was transferred to Fernando Fonseca Hospital. I had no muscle strength and I was confined to bed due to polymyositis. I could not breathe on my own and had to use BiPAP. I was also being fed by a nasogastric tube. After a thorough evaluation of my disease, RTX was given. I began to improve a couple of weeks later. The need for supplementary oxygen decreased and I felt a great desire to eat, something I was not able to do until that date. My recovery was extraordinary after starting RTX, cyclophosphamide and physiotherapy. I can now play football with my son.

Learning points

- Inflammatory myopathies are a very heterogeneous group of illnesses that can present themselves with a very different clinical phenotype.
- Antisignal recognition particle antibodies-associated myopathy is a rare form that can be life-threatening.
- Despite the seriousness of the clinical features of this disease, irreversibility may not be present and a comprehensive approach in a specialised centre may result in an important or even complete recovery.
- Rituximab (together with cyclophosphamide) can be an important option in the treatment of these diseases and can induce a good clinical response and even long-lasting clinical remission.

Competing interests None declared.

Patient consent Obtained.

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