

## Anti-signal Recognition Particle-positive Juvenile Polymyositis Successfully Treated with Rituximab

To the Editor:

Juvenile polymyositis (PM) is a rare form of idiopathic inflammatory myositis (IIM) in children, accounting for 2%–8% of cases<sup>1,2</sup>. In contrast to juvenile dermatomyositis (DM), the characteristic rashes are absent. Myositis-specific antibodies (MSA) can be used to further classify IIM. Anti-signal recognition particle (SRP) antibody is present almost exclusively in PM, and is usually associated with a necrotizing myopathy with a severe or fulminant course and a poor response to therapy<sup>3</sup>.

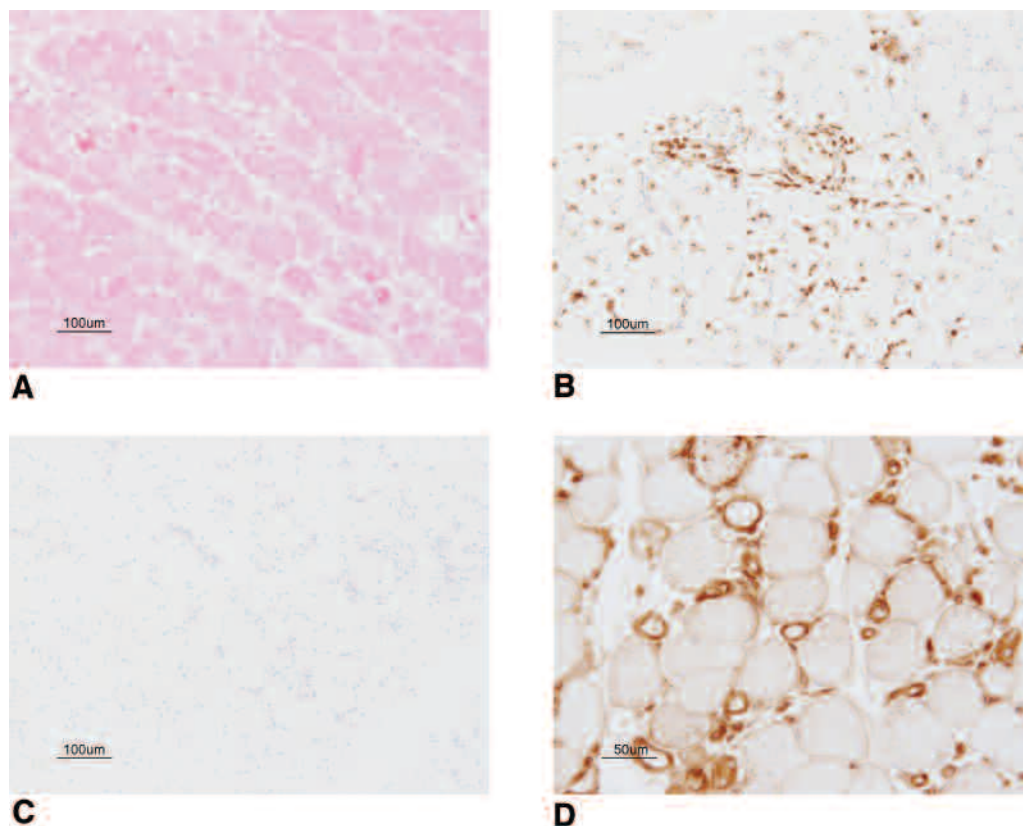
A previously healthy 12-year-old girl presented with a 1-month history of increasing proximal muscle weakness, alopecia, dysphagia, and Raynaud's phenomenon. There was no history of rash or skin changes. On examination, she had visible wasting of her shoulder muscles, manual muscle testing (MMT) of 3/5 in a proximal distribution, and a Childhood Myositis Assessment Scale (CMAS)<sup>4</sup> score of 15/52. There were no skin findings associated with juvenile DM. Serum inflammatory markers were normal. Muscle enzymes were elevated (creatinine phosphokinase 8826 U/l, lactate dehydrogenase 4305 U/l, aspartate aminotransferase 368 U/l), and electromyography demonstrated an active myopathic process. Magnetic resonance imaging (MRI) of the shoulder and hip girdles revealed symmetrically increased T2 signal in hip adductors and shoulder muscles. Pulmonary function tests demonstrated a mild chest wall restrictive pattern with normal carbon monoxide diffusion capacity. Electrocardiogram and echocardiogram were normal. The muscle biopsy (Figure 1A–1D) showed a mixed lymphocytic infiltrate (mostly CD4+ T cells and occasional B

cells) within the endomysium and the perimysium and presence of MHC class I, as well as many atrophic muscle fibers. Some fascicles demonstrated a macrophage infiltrate and fiber necrosis. Immunohistochemical staining for dysferlin, calpain-3, and dystrophin was normal. No tubular reticular inclusions were seen on ultrastructural examination. The pathology was most consistent with a diagnosis of juvenile PM. MSA were requested, and a positive result was obtained for anti-SRP antibodies. Anti-Mi2 and anti-synthetase antibodies were negative.

Treatment was initiated with a 3-day course of pulse intravenous (IV) methylprednisolone 30 mg/kg, followed by high-dose oral prednisone 20 mg 3 times daily, azathioprine 100 mg daily, and weekly subcutaneous methotrexate 20 mg. After 7 weeks of therapy, she had significant difficulty ambulating, and her CMAS score had dropped to 3/52. Muscle enzymes had improved but not normalized. At this time, treatment with IV immunoglobulin (IVIG) was added. Two months later there was mild improvement in CMAS score to 6/52 and muscle enzymes had normalized. Over the next several months, a slow increase in strength was noted, with some ability to ambulate without assistance and climb stairs. MMT for proximal muscles remained 3/5. CMAS score improved steadily to 31/52 and prednisone was tapered.

One year after presentation, she had worsening of muscle weakness and difficulty swallowing. Muscle enzymes again were elevated. She was treated with rituximab (RTX; 500 mg/m<sup>2</sup> × 2 doses, 14 days apart). One month later, lymphocyte immunophenotyping demonstrated absence of CD20+ and CD19+ cells. She did not experience any adverse events related to RTX therapy.

She was maintained on leflunomide, azathioprine, and monthly IVIG.



**Figure 1.** Proximal muscle biopsy of 12-year-old female with profound muscle weakness. A. H&E stain shows variability in fiber size, scattered atrophic fibers, and an endomysial and perimysial inflammatory infiltrate (original magnification ×100). B. CD43 immunohistochemical stain highlights the endomysial and perimysial T cell infiltrate (original magnification ×100). C. CD20 immunohistochemical stain shows a relative paucity of B cells (original magnification ×100). D. MHC class I is expressed on most muscle fibers (MHC class I immunostaining; original magnification ×200).

Over the next months she showed marked clinical improvement and was able to participate in dance classes. MMT improved to 4/5 throughout, CMAS score increased to 46/52, and muscle enzymes stabilized in the normal range (Figure 2). Leflunomide was discontinued 29 weeks after onset of illness. Repeat MRI with short-tau inversion recovery showed resolution of muscle inflammation, with muscle atrophy and fatty replacement. Roughly 2 years after receiving RTX, MSA testing was repeated and anti-SRP was positive (titer not available). However, lymphocyte immunophenotyping showed persistent absence of CD19+ B lymphocytes and she remained clinically well.

Juvenile PM is a rare form of IIM in children. Adult studies of anti-SRP myositis show that this group of patients typically have PM with an increased rate of dysphagia, severe muscle atrophy, and rapidly progressive muscle weakness<sup>5,6</sup>. Many patients are resistant to treatment; in one study 63% required at least 3 drug trials and combination therapy<sup>6</sup>. A pediatric case series described 3 adolescent girls with anti-SRP juvenile PM<sup>7</sup> with profound muscle weakness, internal organ involvement (cardiac and interstitial lung disease), and poor response to multiple therapies. Similar to our patient, 2 of the pediatric patients had an inflammatory infiltrate along with necrosis on muscle biopsy.

Standard therapy for North American patients with juvenile IIM consists of high-dose corticosteroids and methotrexate, with IVIG used as adjunctive treatment for steroid-resistant or steroid-dependent disease. Other medications including cyclosporine, azathioprine, and cyclophosphamide have shown some benefit for refractory disease<sup>8</sup>. More recently, RTX, an anti-CD20 monoclonal antibody, has been tested in patients with refractory IIM. Case series of adults with DM and PM have suggested some efficacy of RTX<sup>9,10,11</sup>. Similarly, series of pediatric patients with refractory juvenile DM treated with RTX report remission in a subset of patients<sup>12,13</sup>. A randomized trial of RTX for both adults and children with myositis has been reported but not yet published<sup>14</sup>.

In adults with refractory anti-SRP myopathy, a retrospective study demonstrated improvement in muscle strength in 6 of 8 patients after treatment with RTX, and a decrease in anti-SRP level in 4 of 5 patients who were tested<sup>15</sup>. Similarly, another case series showed a correlation between anti-SRP antibody titer and level of creatine phosphokinase<sup>16</sup>. Thus, it is probable that the anti-SRP antibodies have a pathogenic role in the inflammatory process. Anti-SRP antibodies in our patient remained present after treatment; however, we did not have access to antibody titers. It is also pos-

sible that the efficacy of RTX is partially due to decreased activation and differentiation of T cells<sup>17</sup>.

We describe a patient with refractory juvenile PM and anti-SRP antibodies with a sustained clinical response to RTX. RTX may be an effective treatment option in cases of anti-SRP-positive IIM.

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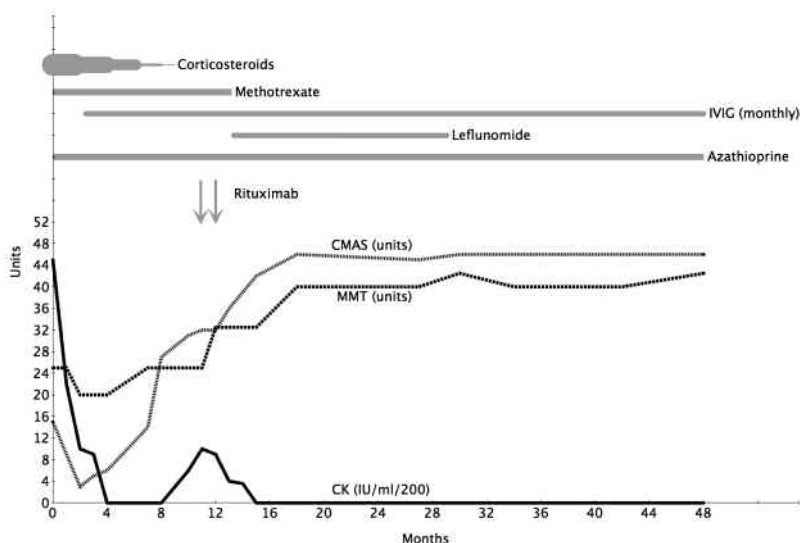


Figure 2. Clinical features of this case over time, indicating trend in creatine phosphokinase (CK) levels, Childhood Myositis Assessment Score (CMAS), and manual muscle testing (MMT).

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