Successful recovery of anti-SRP myopathy with subcutaneous methotrexate after 17 years of poor response to immunomodulation

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ABSTRACT

An 18-year-old woman presented with a year of progressive proximal limb weakness. Serum creatine kinase (CK) was elevated and electromyography suggested an irritable myopathy. Muscle biopsy revealed severe, chronic, active, necrotizing myopathy. Myositis-specific autoantibodies were initially negative; however, an immune-mediated necrotizing myopathy was suspected. She had only minimal response to variable immunomodulatory therapies over 17 years, with progression of weakness. Subsequent repeat testing confirmed positive anti-Signal Recognition Particle (SRP) autoantibodies. A thigh MRI, 17 years after symptom onset, showed extensive fatty replacement and significant muscle atrophy, suggesting a low likelihood of response to further immunosuppression. Nonetheless, motor function significantly improved after initiation of subcutaneous methotrexate (MTX). She has been stable off immunosuppressive therapy for 4.5 years. This report exemplifies that a protracted clinical course, extensive fatty replacement and atrophy on muscle MRI and normal CK levels do not preclude a late response to immunomodulatory therapy in anti-SRP myopathy.

Introduction

Anti-Signal Recognition Particle (SRP) myopathy is an immune-mediated necrotizing myopathy (IMNM) characterized by rapidly progressive proximal and symmetrical weakness that can result in severe disability and a markedly elevated serum creatine kinase (CK).[1,2] Muscle biopsy typically shows prominent muscle cell necrosis and only minimal lymphocytic infiltration.[3] Treatment usually requires long-term use of multiple immune therapies, with the prognosis being worse in those with a younger age of onset.[4] There has been growing evidence regarding the utility of muscle MRI in the management of autoimmune myopathy.[5] It has shown to be a useful tool to monitor the evolution of muscle disease over time and also to determine the optimal location for muscle biopsy to increase its diagnostic yield.

Case Report

An 18-year-old woman, who was previously healthy, except for a 5-year history of complex partial epilepsy that was managed with lamotrigine, presented with a 1-year report of progressive proximal limb muscle weakness. She was unable to dress, cut food, or stand from a chair without assistance. On examination, she had symmetric Medical Research Council (MRC) grade 3/5 weakness in deltoids, biceps, triceps, hip flexors, and knee extensors. Muscle bulk and tone were normal. Deep tendon reflexes were grade 1 at the knees and ankles, and grade 2 in the upper limbs. She had a waddling gait with hyperlordosis and bilateral circumduction. The rest of the neurological examination was normal. Serum CK was 4,384 units/L on presentation. Electrophysiologic testing was consistent with an irritable myopathy with abnormal insertional activity, fibrillation potentials, myopathic motor unit morphology, and early recruitment in the left biceps, infraspinatus, vastus medialis, tensor fasciae lata, and iliopsoas muscles. Nerve conduction studies were normal. A left quadriceps muscle biopsy revealed multiple necrotic and split fibers supportive of a severe necrotizing myopathy without evidence of invasion of non-necrotic muscle fibers (Figure 1). Minimal endomysial and perimysial inflammatory cell infiltrates were noted comprised mainly of CD68 positive macrophages. Blood vessels showed a normal pattern of staining with Eulex Europaeus (lectin) and membrane attack complex (MAC) relative to controls, but some non-necrotic muscle fibers showed MAC sarcolemmal staining. Immunohistochemical stains for dystrophin, sarcoglycanopathy, dysferlin, and merosin showed a normal pattern. Genetic testing was negative for pathogenic mutations in the FKRP, CAPN3, CAV3, and LMNA genes. Autoantibodies included negative antinuclear antibody, rheumatoid factor, anti-RNP, Smith, Jo-1; Subsequent further testing for

myositis-specific antibodies, including PL 7, PL-12, MI-2, KU, EJ, and OJ, was also unrevealing; however, an immune-mediated necrotizing myopathy was clinically suspected.

Axial T1 weighted MRI of bilateral lower extremities, obtained 4 years after symptom onset, showed evidence of diffuse fatty infiltration of bilateral thigh musculature, with abnormal high signal on inversion recovery sequences within the muscles of the anterior and posterior compartments of bilateral thighs and gastrocnemii. Diffuse enhancement was seen, most prominently in the quadriceps muscles following gadolinium administration. The patient was variously treated with regimens including corticosteroids (both daily oral prednisone [1mg/kg] and intermittent intravenous high dose methylprednisolone), intravenous immunoglobulin (IVIG), subcutaneous MTX that was only briefly used and stopped due to severe diarrhea, azathioprine, mycophenolate, extended courses of plasma exchange (PLEX), and rituximab. She had only transient and suboptimal responses to immunomodulatory therapy over 16 years, with progression of weakness and disability requiring a wheelchair, and multiple hospitalizations for exacerbations including respiratory impairment which did not require intubation. Dyspnea did subjectively improve with immunotherapy during hospitalizations.

Laboratory testing at age 30 years confirmed the presence of anti-SRP autoantibodies on a radioimmunoprecipitation assay. Anti-HMG-CoA reductase antibodies were negative. The patient, who was on prednisone and azathioprine at the time, received further intensive prolonged courses of PLEX with only a minimal response. There was also no response to another trial of rituximab.

A subsequent thigh MRI at age 33 years showed extensive fatty replacement and muscle atrophy (Figure 2). Muscle edema was noted though this was difficult to interpret due to the significant muscle atrophy. In light of the patient's MRI findings and normal CK of 125 U/l, a response to further immunosuppression was considered unlikely. Nonetheless, due to the patient's continued declining function, subcutaneous MTX (titrated to 12.5 mg weekly subcutaneously) along with weekly folinic acid 10 mg by mouth (because of prior GI intolerance of MTX) was added to her existing regimen of prednisone (45 mg by mouth daily) and azathioprine (125 mg by mouth total daily dose). Within a few months after initiation of MTX, motor function had significantly improved with recovery of independent ambulation. On examination, Medical Research Council (MRC) grade had improved to 4-5 in the biceps, knee flexors, and knee extensors. The patient weaned herself off all immunosuppressive therapy at age 35 years. She has subsequently been functionally stable off all immunosuppressive therapy for the past 4.5 years.

Discussion

This report of a patient with severe, SRP-related necrotizing myopathy is instructive, in that the patient had been relatively refractory to a multitude of immunosuppressive regimens over 17 years, with only transient or limited responses, normal CK, and a muscle MRI showing marked fatty replacement, suggesting a low likelihood of treatment responsiveness. She nonetheless showed marked functional improvement with the late initiation of subcutaneous MTX and folinic acid.

The initial clinical presentation was typical of anti-SRP myopathy with subacute severe proximal muscle weakness and significantly elevated CK levels without skin involvement. Although anti-SRP myopathy is more commonly seen after the fourth decade, younger onset including childhood or adolescence has been reported.[6-8] The presence of SRP autoantibodies is essential for diagnosis, as this form of myopathy is often clinically or pathologically indistinguishable from other types of autoimmune myopathy. For example, muscle necrosis can be observed in multiple other types of myopathy including dermatomyositis, anti-Jo1 antisynthetase syndrome, scleroderma-myositis, and various hereditary myopathies, while perivascular infiltrates can be seen in anti-SRP myopathy.[5,9] Binns et al. reported in their case series and literature review of childhood or juvenile-onset anti-SRP myopathy that the long-term functional outcomes are generally poor with severe residual weakness in 50% of 12 patients and wheelchair dependence in 40%.[6] Also, in a longitudinal cohort study of 37 adults with anti-SRP myopathy, younger age at onset was associated with more severe muscle weakness at initial and follow-up visits.[10]

Muscle MRI has been used to detect muscle edema, fatty replacement, and atrophy using both T1 weighted and short tau inversion recovery (STIR) sequences. Active muscle edema due to inflammation or myofiber necrosis appears as intramuscular hyperintensities on STIR sequences and fatty replacement is best seen for clinical purposes on T1-weighted images. In IMNM, MRI findings are characterized by a higher proportion of thigh muscles with edema, atrophy, and fatty replacement.[11,12] Thigh muscle edema on MRI was identified in each of the 12 reported patients with anti-SRP myopathy including in the vastus lateralis, rectus femoris, biceps femoris, and adductor magnus muscles.[13] Anti-SRP myopathy usually shows a more severe pattern of muscle involvement on MRI than HMG-CoA reductase antibody-related IMNM.[10] It is considered that muscle edema seen in necrotizing myopathies is likely of osmotic origin rather than inflammatory cell infiltration, given that there are typically minimal inflammatory cells in the muscle biopsy.[13] Intramuscular fat accumulation is considered an indicator of irreversible consequences of the myopathic process while muscle edema has been suggested to indicate potential reversibility with treatment in autoimmune myopathy.[5,13] A longitudinal study observed, as in our patient, that with an increasing interval between onset of disease and timing of muscle MRI, patients showed greater fatty replacement and less muscle edema.[11] Furthermore, in

the study by Zheng et al, there was a negative correlation between the degree of muscle fat accumulation and therapeutic effect.[13] The mechanism for the marked improvement seen in our patient after 17 years of disease despite marked muscle fat replacement and a low CK value is uncertain. Notwithstanding the persistence of some muscle edema, our patient's late response to treatment serves to indicate that muscle MRI findings of marked fat replacement and muscle atrophy may not be relied on alone to guide the likelihood of therapeutic response in anti-SRP myopathy but are rather a helpful adjunct in the therapeutic decision-making process.

The underlying pathogenesis of anti-SRP myopathy is unknown but is probably due to a combination of immune-mediated and environmental and genetic factors. Multiple pathways have been implicated in the pathogenesis of muscle destruction in anti-SRP myopathy, including direct pathogenic effects of anti-SRP autoantibodies, complement-dependent mechanisms, altered cytokine and chemokine milieu, and upregulation of B-cell activating factor.[14] In terms of treatment approach, our patient showed a clinically significant late improvement with the introduction of MTX. In 2017, a European NeuroMuscular Centre (ENMC) working group recommended corticosteroids and MTX as a first-line treatment regimen for anti-SRP myopathy.[4] A 16-patient retrospective case series supports the effectiveness of MTX for anti-SRP myopathy. Thirteen of these individuals received oral prednisone and MTX and showed a degree of improvement.[15] The mechanism of treatment of SRP myopathy with MTX is unknown but may relate to both anti-inflammatory and immune-modulating properties. These may include inhibition of anti-inflammatory adenosine metabolism, which leads to reduced T-cell activation, down-regulation of B cells, increased activated CD-95 T-cell sensitivity, and inhibition of the binding of pro-inflammatory beta-1 interleukin to its cell surface receptor.[16] An ENMC working group has also recommended rituximab as an alternative approach.[4] In contrast to our patient who failed to respond to 2 separate trials of rituximab, 76.5% (13/17) of patients with anti-SRP myopathy who received rituximab, showed responsiveness in one longitudinal cohort study.[14] Similarly, a literature review reported that 77.8 % (14/18) of patients with anti-SRP myopathy showed a response to rituximab.[12] Rituximab, as a B cell depleting agent, may be an effective treatment for refractory SRP myopathy due to its effects on anti-SRP autoantibodies, which play a role in both the formation of atrophic muscle fibers and muscle fiber regeneration.[14] Allenbach et al. and others have described that individuals with anti-SRP myopathy treated with IVIG, more frequently achieve remission than those not receiving IVIG therapy.[4, 17] Our patient did not show an appreciable response to IVIG. Thus, response to immunomodulatory therapy appears quite non-uniform among those with anti-SRP myopathy, possibly reflecting diversity of disease mechanisms.

Conflict of interest

Alexis Lizarraga reports no disclosures.

Yohei Harada is a salaried employee of UCB Pharma and receives stock and stock options from employment. The research presented in this publication was conducted outside of the scope of current role in the company. The views and opinions expressed in this publication are solely those of the authors and do not necessarily reflect the official policy or position of the company.

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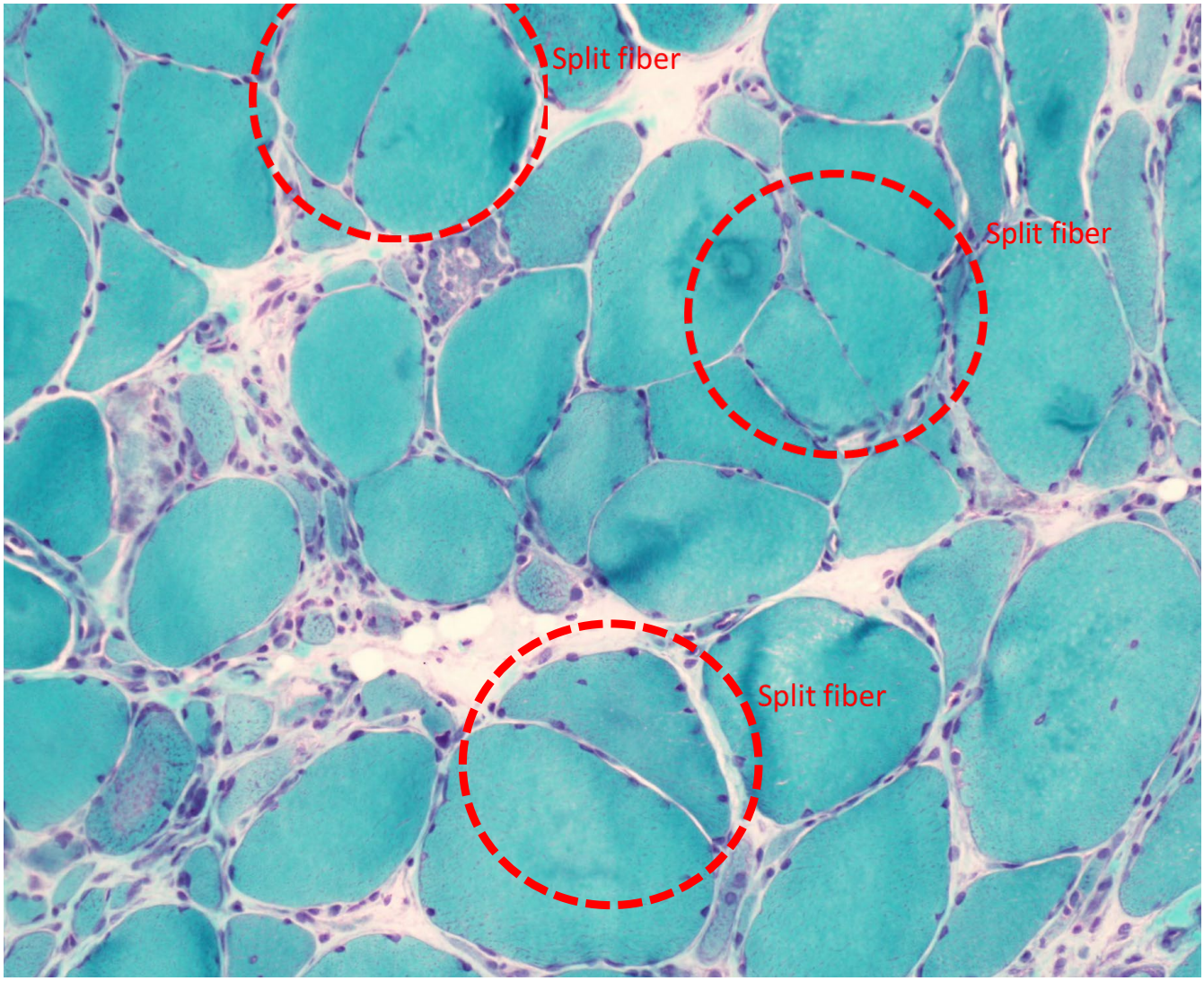

Figure 1: Left quadriceps muscle biopsy (Gomori trichrome stain):
Moderately severe, chronic, active myopathy as evidenced by increased muscle fiber size variability, split fibers, and rounded fibers with internal nuclei. Though not seen in this slide, there was minimal necrosis surrounded by macrophages There were minimal perivascular and endomysial mononuclear inflammatory cell infiltrates. No ragged-red fibers were present.

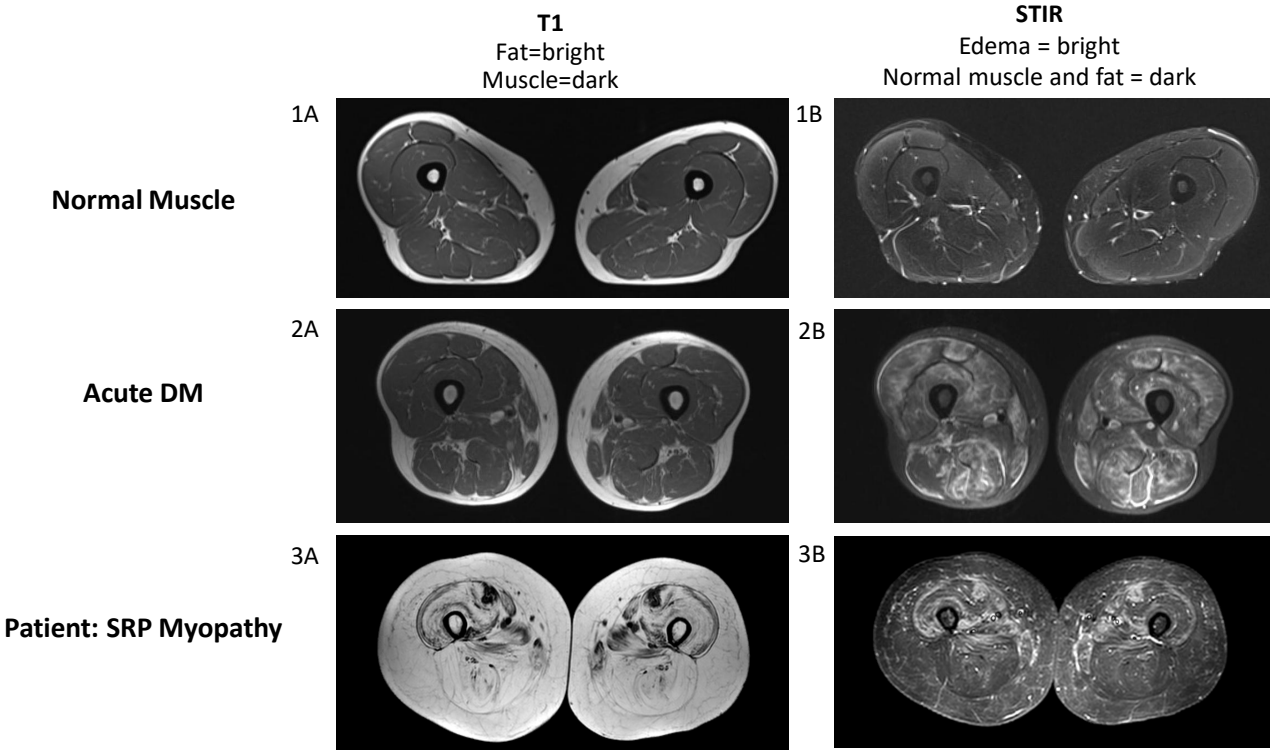

Figure 2: Muscle MRI of right and left thighs with comparison cases
(1A) Normal Axial T1 MR sequence, (1B) Normal Axial STIR MR sequence, (2A) Axial T1 MR sequence in acute dermatomyositis (DM) showing normal muscle bulk without fatty replacement, (2B) Axial STIR MR sequence in acute DM showing diffuse hyperintensity indicating muscle and fascial edema, (3A) Axial T1 MR sequence showed diffuse hyperintensity suggestive of extensive atrophy and fatty replacement of muscle, (3B) Axial STIR MR sequence demonstrated hyperintensity of the right anterior thigh muscles suggesting edema.