Case Report

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Treatment of refractory immune-mediated necrotizing myopathy with abatacept and tacrolimus: A case-based review

Idiopathic inflammatory myopathies are characterized by muscle weakness, elevation in serum muscle enzyme levels, electromyography abnormalities, presence of Myositis Specific Autoantibodies (MSAs) and findings of inflammation on muscle biopsy. Immune-mediated necrotizing myopathy (IMNM) is a subset of IIM that is often resistant to standard immunosuppressive therapy, requiring multiple combinations of therapeutic agents. We present a case of a middle-aged man with positive anti-Signal Recognition Particle (SRP) IMNM who responded to abatacept and tacrolimus after failing standard of care treatment.

Keywords: idiopathic inflammatory myopathies • abatacept • tacrolimus

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Introduction

Idiopathic inflammatory myopathies are a group of separate clinicopathological diseases characterized by muscle weakness, elevation in serum muscle enzyme levels, abnormal electromyography, presence of myositis specific antibodies (MSAs), and findings of inflammation on muscle biopsy [1]. The European Neuro Muscular Centre (ENMC) in 2004 proposed the following classification criteria for inflammatory myopathies based on clinical features, laboratory and muscle biopsy findings, dividing them into five categories: Polymyositis(PM), Dermatomyositis(DM), inclusion body myositis (IBM), non-specific myositis, and Immune-Mediated Necrotizing Myopathy (IMNM). According to these criteria, muscle biopsy features are used exclusively to categorize patients as having IMNM [2].

IMNM is a recently recognized separate myopathy that typically presents with proximal muscle weakness, myalgias and markedly elevated Creatine Kinase (CK) levels that are resistant to standard immunosuppressive therapy. Biopsies of skeletal muscle of patients with IMNM show absence or scant inflammatory cells with prominent myofiber necrosis and regeneration, whereas other subgroups of autoimmune inflammatory myopathies have characteristic inflammatory infiltrate on biopsy [3]. The presence of necrosis does not exclude other types of inflammatory myositis [1].

Two different autoantibodies have been recently associated with IMNM: anti-Signal Recognition Particle (SRP) antibody, seen in up to 15% of patients with IMNM, and anti-Hydroxy-3-Methylglutaryl-CoA Reductase(HMGCR) antibody, associated with previous use of statins [4,5]. Benveniste et al. suggested that anti-SRP antibody levels may correlate with the degree of myofiber damage and therefore can be used to assess disease activity [6]. In addition, the presence of these antibodies on muscle biopsy was associated with elevated levels of pro-inflammatory molecules such as IL-6, Tumor Necrosis Factor (TNF) and reactive oxygen species [7].

Treatment of IMNM is challenging as it

is a relatively newly described entity and consensus guidelines are lacking. According to the latest ENMC report on IMNM, the first line treatment is corticosteroids, however most cases are refractory to steroid monotherapy. Decision to add a second agent is based on comorbidities such as diabetes mellitus, osteoporosis and interstitial lung disease, as well as severity of disease and intention to avoid long-term complications of corticosteroid use.

Azathioprine and methotrexate are considered first line steroid-sparing agents, with mycophenolate mofetil being an option if hepatic dysfunction is present [8]. Intravenous immunoglobulin (IVIG) has also shown to be effective in the treatment of anti- SRP myopathy especially when given on a regular basis [9]. Tacrolimus is a calcineurin inhibitor that also inhibits IL-2 gene transcription, cellular apoptosis and nitric oxide synthase activation [10]. According to some studies tacrolimus has been shown to be useful in managing anti-SRP myopathy in combination with steroids [11,12]. Abatacept, a fusion protein of the extracellular domain of the human Cytotoxic T-Lymphocyte-associated Antigen 4 (CTLA-4) inhibitor and the Fc portion of the immunoglobulin IgG1, has been proposed as treatment for anti-SRP myopathy as it reduces the levels of pro-inflammatory cytokines that are responsible for the muscle damage [13,14]. We present an interesting case of a patient with IMNM refractory anti-SRP who responded to the combination of tacrolimus and abatacept.

Case presentation

A 43-year-old Caucasian man with a diagnosis of anti-Signal Recognition Particle (SRP) positive myositis presented to the rheumatology clinic for treatment discussion.

He was diagnosed with presumed psoriatic arthritis before establishing care in our clinic and was treated with oral methotrexate and infliximab infusions without improvement. Etanercept provided a partial response and it was discontinued. Magnetic Resonance Imaging (MRI) of bilateral thighs was done due to severe proximal lower extremity weakness. It showed muscular edema involving the vastus medialis, vastus lateralis, gluteus maximus, obturator externus, pectineus adductor brevis and iliopsoas muscles. Muscle biopsy was pursued and revealed necrotizing myopathy.

Laboratory studies revealed a positive anti-Sjogren's-syndrome-related antigen A (SSA) antibody, positive anti-centromere antibody, positive anti-scl-70 antibody and positive anti-Jo antibody. Anti-SRP antibody was also positive. Aldolase and creatine kinase were markedly elevated. The patient had normocytic anemia with elevated Erythrocyte Sedimentation Rate (ESR).

Azathioprine was initiated along with high-dose oral prednisone. He developed generalized maculopapular rash with azathioprine, and the medication was discontinued. Subsequently, Intravenous Immunoglobulin (IVIG) in combination with cyclosporine was started with an improvement of 80% of his extremity weakness. Mycophenolate mofetil was added to his regimen. The patient sought a second rheumatologic opinion and established at our clinic. He reported persistent proximal extremity weakness predominantly in quadriceps and deltoids, bilateral hand and foot pain. He denied any skin rash, oral or nasal ulcers, dyspnea, chest pain, weight loss, fever, night sweatsor dysphagia. He was on oral prednisone 30 mg daily and was unable to taper it lower than this dose without worsening of weakness. After reviewing his previous medical records, performing a comprehensive physical exam demonstrating bilateral proximal muscle weakness in quadriceps and deltoids, and elevated muscle enzymes and positive anti-SRP antibody, we made the diagnosis of IMNM.

While IVIG was initially effective, it lost its efficacy and thus was discontinued. Rituximab was initiated. This medication did not improve the patient's symptoms andwas discontinued. Then Adrenocorticotropic Hormone (ACTH) gel injection was given with a satisfactory initial response but after two months it lost efficacy and was discontinued. At this time, a change in his medication regimen was made, and oral cyclophosphamide was administered. The patient reported significant improvement of his weakness and pain for the first time in many years. He was transitioned to tacrolimus with oral prednisone however due to a non-tuberculous mycobacterium skin infection, cyclophosphamide was discontinued. Tacrolimus dose was adjusted multiple times and cyclophosphamide was stopped. To taper down the prednisone, he was switched to methylprednisolone however he still had difficulty with doses less than 20 mg daily. He was then started on abatacept 125 mg subcutaneous once weekly, in addition to tacrolimus 2 mg twice daily and has managed to decrease his methylprednisolone to below 10mg daily. The patient had a great serologic and clinical response to this combination. His muscle enzymes decreased considerably, and his proximal lower extremity strength improved.

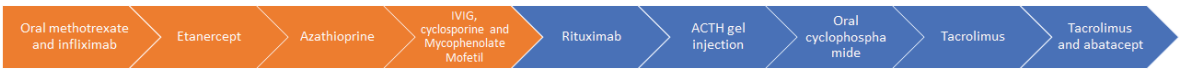

Figure 1. Timeline highlighting the different treatment modalities that the patient received. The orange color represents the treatments prior to establishing in our clinic, and blue color represents the treatments in our clinic.

Discussion

Immune-Mediated Necrotizing Myopathy (IMNM) is a recently described entity that was separately classified from the other types of IIM in 2004 given the presence of prominent myofiber necrosis [2,3]. The pathophysiological mechanism is not well understood, and it appears that statins play an important role in the subset of anti-HMGCR antibody positive myopathy. IMNM must be differentiated from other myopathies such as drug-induced myopathy and endocrinopathies such as hypothyroidism [15]. In our patient, steroid-induced myopathy was considered given the long-standing use of high doses of prednisone, however patient's symptoms and laboratory values worsened with attempts to taper oral steroids.

The therapeutic decisions and recommendations for the treatment of IMNM are mostly based on documented case series, the expertise of the clinician and other observational studies. Like other forms of myositis, the aim is to treat rapidly progressive myositis with most intensive therapy [11,16]. Despite corticosteroids being the first line treatment option per the ENMC guidelines, most cases are refractory to steroid monotherapy [17].

Most favorable outcomes are obtained when patients are treated with combined immunosuppressive therapy compared to the use of steroids alone [4,11,15,18,19]. Methotrexate alone or in combination with Rituximab has been shown to improve symptoms as well as reduction of anti-SRP antibody levels in refractory cases [20]. Our patient failed or developed side effects to multiple immunosuppressant agents, including methotrexate, infliximab, azathioprine, IVIG, cyclosporine, rituximab, mycophenolate mofetil and cyclophosphamide (**Figure 1**).

The use of tacrolimus in combination with steroids in cases of refractory anti-SRP myopathy has been described with success. Our patient had symptomatic improvement with tacrolimus and cyclophosphamide however he experienced multiple infections. Cyclophosphamide was discontinuedand tacrolimus dose was adjusted to lower levels, but this regimen did not maintain remission.

Subsequently, abatacept was added to his regimen. Some case series have shown efficacy of abatacept in refractory inflammatory myositis [21]. This drug inhibits T-cells and reduces migration into B cell follicles causing a reduced antibody response [14]. There is very limited data on the efficacy of abatacept in the management of anti-SRP myopathy. To our knowledge, Maeshima et al. reported the only case of a patient with anti-SRP myopathy treated with abatacept in combination with tacrolimus [22]. Currently, there is an ongoing stage 3 clinical trial for the use of abatacept in adults with active idiopathic inflammatory myopathy (ClinicalTrials.gov Identifier: NCT02971683). In this study, patients with IMNM are included.

Conclusion

Immune-Mediated Necrotizing Myopathies (IMNM) are a subset of immune inflammatory myopathies that includes anti-SRP myopathy. There are no clear guidelines to their treatment and it usually involves multiple immunosuppressant agents. Our case highlights that patients with refractory anti-SRP myopathy may benefit from the unique combination of abataceptwith tacrolimus). Currently, there is an ongoing clinical trial that will assess the efficacy of abatacept with idiopathic inflammatory myopathies.

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Authors' contributions

All authors contributed to the creation of this manuscript.

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