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CASE REPORT

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Anti-HMG-CoA reductase myopathy, an undesirable evolution of statin induced myopathy: a case report

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ABSTRACT

Statins are commonly used lipid lowering agents which play a pivotal role in reducing cardiovascular morbidity and mortality. Often well tolerated, these HMG-CoA reductase (HMGCR) inhibitors can sometimes cause severe muscle weakness and elevated creatinine kinase (CK) often labeled as statin intolerance or statin induced myopathy. These symptoms improve after discontinuation of the offending drug along with normalization of the enzyme levels. However, an entity called Immune Mediated Necrotizing Myopathy (IMNM), a type of autoimmune mediated myopathy, has been recognized and characterized in patients with history of statin exposure where there is persistence of proximal muscle weakness, CK elevation and myofiber necrosis can be seen on muscle biopsy even after stopping statins. With the increased use of statins, there seems to be a higher incidence of IMNM cases in recent years. Here we discuss a case of anti-HMG-CoA myopathy, one of the three recognized types of IMNM that has been more commonly associated with statin exposure and highly responsive to immunotherapy.

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1. Introduction

Idiopathic inflammatory myopathy (IIM) is a group of rare, chronic autoimmune disorders which commonly includes polymyositis (PM), Dermatomyositis (DM) and Inclusion body myositis (IBM). Sometimes considered as a type of Polymyositis, Immune Mediated Necrotizing Myopathy (IMNM) has been identified as an important and separate entity of Idiopathic Inflammatory Myopathy. IMNM is characterized by severe proximal muscle weakness, markedly elevated Creatinine Kinase (CK) and myofiber necrosis with no or minimal inflammatory cell infiltrates on muscle biopsy. Three different subtypes of IMNM based on serology have been described in many literature and recognized by European Neuromuscular Centre [1]. These include Anti-signal recognition particle (anti-SRP) myopathy, Anti-hydroxy-3-methylglutaryl-coenzyme A reductase (anti-HMGCoA reductase) myopathy and autoantibody negative myopathy [1,2]. These conditions, which differ in clinical and pathophysiological features have a combined incidence rate of 4 cases per 100,000 person-years [3]. While actual incidence rate of statin induced IMNM is not known, studies have shown that 6% of all patients with suspected immune-mediated myopathy who underwent [4,5] muscle biopsy were found to have positive anti-HMGCR antibodies in which upto 80% had been exposed to statins [3].

Anti-SRP myopathy [6] patients have more severe muscle weakness and often poor outcome even with treatment. This is a rapidly progressing and most disabling kind of autoimmune myopathy which usually presents with skin, cardiac or pulmonary involvement. In contrast, anti-HMGCR myopathy is mostly seen in the setting of statin exposure and less commonly has extra-muscular involvement [1,2]. Autoantibody-negative autoimmune necrotizing myopathy remains poorly described, but they present with similar clinico-pathological features but lack the autoantibodies. Although all three IMNM can be associated with cancer, the seronegative patients have the highest malignancy risk.

2. Case description

A 54 year old Caucasian woman presents to the Emergency room with progressive fatigue and proximal muscle weakness for two months. She had history of hypertension, type 2 diabetes mellitus and hyperlipidemia. She was on atorvastatin for the last 4 years. Her initial blood work was flagged with markedly elevated CK levels of 16,000 Units/Liter, which triggered admission for statin induced rhabdomyolysis. Her CK levels did not improve and her symptoms continued to worsen despite aggressive hydration. Eventually an MRI of the lower extremities was done which showed multifocal edema and enhancement of bilateral thigh muscle. Suspecting inflammatory myositis, a biopsy of the thigh muscle was done which showed mild to moderate necrotizing myopathy with myofiber degeneration and necrosis and myophagocytosis highlighted on the acid

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phosphatase, MHC-1 and CD68, CD8, CD3 stains. Serology showed positive ANA, HMC-CoA ab and anti-Ro antibodies. Diagnosed as anti-HMG-CoA type of Immune mediated necrotizing myopathy, the patient was trialed on methotrexate (MTX) 15mg and prednisone 40mg orally without improvement and severe gastrointestinal upset after the MTX. The patient was then started on high dose pulse methylprednisolone 1g for 3 days followed by intravenous immunoglobulins (IVIG) for 5 days. Her CK dropped from 16,000–3000. However, her condition was complicated by diabetic ketoacidosis (DKA) and mild oropharyngeal dysphagia noted on fluoroscopic study. A pulmonary function test (PFT) showed mild restrictive disease. A transthoracic echocardiogram (TTE) showed no cardiomyopathy. With mild improvement of her symptoms, the patient was discharged on azathioprine 50 mg and prednisone 60 mg orally to taper. She was discharged to a sub-acute rehabilitation center with significant objective improvement in terms of muscle strength and muscle endurance. The patient was then scheduled for a biweekly IVIG infusion with a goal to taper off prednisone, and eventually space out IVIG infusion and continue on azathioprine for long term management. After 6 months of treatment including rehab and home physical therapy, her CK levels dropped to 155 Units/Liter and she went from a Hoyer lifter to walking with a cane.

3. Discussion

Necrotizing myositis or Immune mediated necrotizing myopathy (IMNM) is a disabling type of auto-immune myopathy characterized by severe muscle weakness, markedly elevated CK and muscle necrosis. It is now well recognized to include at least three distinct serologically defined subtypes: anti-SRP myopathy, anti-HMGCR myopathy, and antibody-negative IMNM. Although they all have myofiber necrosis as the predominant histological feature on muscle biopsy, they vary on environmental risk factors, one of which is statin exposure, more commonly seen in Anti-HMGCR myopathy [7]. Interestingly, the duration of statin does not seem to affect the development of myopathy, and in some patients, the myopathy has developed after discontinuation of the statins [8]. CK can be used to assess flare-ups in most of the cases. However, in long standing or poorly treated disease, muscles are replaced by fat and connective tissue, thus CK may be normal despite severe symptoms. In such cases, muscle magnetic resonance imaging (MRI) is the best way to assess the disease progression. Short tau inversion recovery (STIR) signal is usually increased more diffusely and may be asymmetric and T1 hyper intensity reflects connective tissue and fatty replacement in the muscle [7]. MRI also helps the surgeon to target muscle with edema which is the preferred biopsy location. Biopsy shows muscle cell necrosis, muscle cell regeneration, class I MHC up regulation and deposition of Membrane attack complex (MAC) on the sarcolemma of the non-necrotic muscle fibers. Electromyography (EMG) may be useful in early diagnostic workup to look for myopathic pattern and to rule out other neuropathy or Myasthenia Gravis. Pulmonary function test (PFT) and high resolution computed tomography (HRCT) can be performed if there is suspicion of lung involvement [1].

The Anti-SRP myopathy is common in younger population. The age of onset is usually after the fourth decade and manly affects females. These patients commonly have dysphagia, cardiac involvement in the form of rhythm or conduction abnormalities and occasionally cardiomyopathy [2]. Interstitial lung disease occurs in about one third of the patients. The titers of SRP antibody levels correlate with serum CK levels. The outcome of anti-SRP myopathy is poor, as only half of these patients recover normal strength after 4 years of treatment [2].

The exact cause of IMNM is not known, however immunogenetics testing show association with HLA-DRB1*11: 01 and HLA-DRB1*07: 01 alleles which have been reported particularly in patients with anti-HMGCR myopathy [7]. A study by Amato and colleagues reported 25 patients with an age of onset of 64.7 years who developed a necrotizing myopathy in the setting of statin treatment. They manifested proximal muscle weakness and elevated CK levels (mean CK 8203 U/L) that persisted or worsened despite discontinuation of the drug (mean CK 6896 U/L off statin before treatment) and improved following immunotherapy (mean CK 1052 U/L) [2]. Most patients relapsed when tapered off of immunotherapy. Furthermore, to support the statin association, an analysis of database of muscle biopsies showed that exposure to statins prior to onset was significantly higher in the necrotizing myopathies (82%) compared to patients with dermatomyositis (18%), polymyositis (24%), or inclusion body myositis IBM (38%) [2]. Stine and colleagues identified novel autoantibodies in patients with necrotizing myopathy based on muscle biopsy specimens and serum samples of 225 patients with myopathy. Twenty-six patients with necrotizing myopathies had a unique autoantibody specificity against 200-kd and 100-kd proteins. Patients with 200/100 autoantibody specificity had proximal weakness (100%), high creatine kinase levels (mean 10,333 U/L) and exposure to statins prior to the onset of weakness (63%). The study concluded that patients with necrotizing myopathy who previously were considered to be autoantibody negative have in-fact frequent association with statin use and should be treated with immunosuppressive therapy. A recent study suggested that atorvastatin may be most strongly associated with the development of anti-HMG-CoA reductase myopathy compared to simvastatin or rosuvastatin [2].

Interestingly, statins are also present in food and dietary supplements like Oyster mushroom, red yeast rice and Pu-erh tea, which are common in Asian cooking, suggesting the possibility that Asian population without statin exposure may have higher incidence of anti – HMGCR myopathy [1].

There are no specific guidelines or formal recommendations for treatment of IMNM. However, based on multiple case series, randomized trials and anecdotal reports, first line of treatment remains oral high doses corticosteroids or pulse intravenous methylprednisolone. Some experts recommend intravenous immunoglobulins (IVIG) as first line, especially in anti-HMGCR myopathy and in pregnant and young patients [2]. Azathioprine is the preferred agent with a dose of 3 mg/kg/actual body weight in patients where steroids are contraindicated. Methotrexate (MTX) can be used as an adjunct to azathioprine but both drugs would need frequent monitoring of hepatic function and folic acid supplementation. Rituximab can be considered the third line in treatment of IMNM. There has been considerable experience with rituximab in anti-SRP myopathy and growing use in HMGCR myopathy. If there is concern of hepatic dysfunction, mycophenolate mofetil can be used at a dose of 2–3 grams a day in two divided doses. Other options include cyclosporine, cyclophosphamide and etanercept [2].

The prognosis of IMNM is worse than inflammatory myositis. About 50% of these patients continue to have muscle weakness after 2 years of treatment. Younger patients have worse prognosis and more severe disease compared to those diagnosed at a later age. IMNM patients with either autoantibody may develop dystrophy like features due to early fatty replacement of the muscle, therefore early treatment with immunosuppressants is warranted to prevent long term disability [2]. There needs to be multicenter trials in IMNM to help develop screening tools to identify high risk patients before recommending statins. Furthermore, a standardized protocol to treat such patients is still lacking at this time.

Disclosure statement

No potential conflict of interest was reported by the authors.

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