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## Statin as A Cause Immune-Mediated Necrotizing Myopathy: Case Report and Narrative

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### 1. Abstract

Statin-induced immune-mediated necrotizing myopathy (IMNM) is an exceedingly rare complication of statin use, which should be suspected in the patient with elevated CPK levels, symmetric proximal muscle weakness and persistence of symptoms despite discontinuation of statin therapy. We presents the case of IMNM developed in patient without any personal or family history of autoimmune pathology several month after he was started on atorvastatin therapy. The case presentation includes history of difficult pathway to right diagnosis and description of successful immunosuppression therapy lead to clinical and laboratory recovery. In our narrative review we tried to accumulate the newest data about disease prevalence, clinical presentation, and proposed diagnostic and treatment algorithms. We also tried to gather and aggregate the information about the most likely “culprit” statin types in regard to published reports, and available information about different local statin types preferences.

### 2. Introduction

We present a typical case of statin-induced IMNM with narrative review of epidemiology, classification, types of statin involved, laboratory findings, muscle biopsy results, MRI findings and brief discussion of the management.

### 3. Case Description

Our patient is a 53-year-old male with a past medical history of

long-standing hypertension, type II diabetes mellitus, ADHD, and hyperlipidemia presented as a transfer from an outside hospital for an evaluation of unrelenting elevation of CPK. Initially, the patient presented to the emergency department with complaints of proximal muscle weakness of upper and lower extremities for two months before admission and was found to have an elevated 47 CPK of 24,000

U/L, elevated aldolase, and moderate transaminitis. He was admitted to the hospital and atorvastatin was stopped in light of possible statin-induced myopathy. He was treated with atorvastatin for at least 9 months before discontinuation. His other medications included carvedilol, enalapril, hydrochlorothiazide, glipizide, and metformin. During this hospitalization,

despite vigorous intravenous hydration with normal saline elevation of CPK level up to 27,000 U/L was observed before discharge. Patient reported an improvement in muscle weakness and was discharged home. On his follow up 5 days later, patient reported recurrence of his symptoms and his CPK increased to 41,000 U/L. He was readmitted and treated with intravenous fluids but neither improvement in symptoms nor decline in CPK level was observed. Patient was transferred to our hospital about 3 weeks after initial presentation. He had no known family history of any kind of myopathy. He denied alcohol use in any amount and denied any history of illicit drug use. He also denied having any recent viral illness, and denied any history of recent strenuous exercises or weight lift

ing. Patient reportedly visited West Africa approximately 6 months before admission. His physical examination was mostly remarkable only for symmetrical upper and lower proximal extremity weakness with normal active and passive range of motion, without any tenderness on palpation. No rashes in the arms, eyelids or torso suggestive of Gottron papules. Laboratory studies were significant for CPK of 41,000 U/L, transaminitis (AST 365 IU/L, and ALT 615 IU/L), anemia with hemoglobin level of 10.5 gm/dL, and low WBC level of 3,065 /L. Interestingly, his renal function was not adversely affected, with BUN 9, creatinine level of 0.53, and GFR greater than 110. Because of the unrelenting course of muscle damage despite discontinuation of statin therapy, an HMGR IgG antibody test was performed and found to be positive with a titer greater than 200. For diagnosis confirmation, a muscle biopsy was planned, but prior to muscle biopsy we proceeded with an MRI of the right thigh without contrast as it has been shown to increase the validity of muscle biopsy results. The MRI revealed severe intramuscular edema in the medial, lateral compartments,

and anterior compartments, mostly affecting the rectus femoris muscle belly, and mild areas of interfascial fluid within the medial and posterior compartments. Subcutaneous soft tissue edema was also present diffusely with superficial perifascial fluid throughout the anterior, medial, and posterior compartments of the thigh, which is not specific for any particular type of myopathy. The skeletal muscle biopsy of the right thigh showed no features of chronic remodeling in the form of endomysial fibrosis or fatty replacement. Although no distinct pattern of atrophy was found, mildly atrophic type II fibers as well as a few fibers with features of individual fiber necrosis or regeneration were found. Labeling for MHC1/HLA-ABC showed cytoplasmic and sarcolemmal staining of scattered myopathic fibers as well as cytoplasmic C5b-9 staining was positive within necrotic fibers. Endomysial capillary staining was not significantly increased, with only rare isolated fibers with somewhat granular sarcolemmal staining identified. No rimmed vacuoles with modified Gomori trichrome stain were found. These findings are not associated with any significant inflammatory myopathy and are suggestive of an immune-mediated necrotizing myopathy. According to ENMC criteria, the patient was diagnosed with an anti-HMGR immune-mediated necrotizing myopathy (IMNM). Following current treatment

recommendations, the patient was treated with intravenous pulse methylprednisolone 1g daily for three days with subsequent transition to oral prednisone 60mg daily. Azathioprine 50mg daily was added to the treatment regimen due to low effectiveness of steroid treatment alone with good results. Our patient additionally received *Pneumocystis jirovecii* pneumonia prophylactic treatment with Bactrim DS on an every other day dosing schedule. The CPK level decreased to 22,000 with improvement of symptoms and he

was asymptomatic at discharge with a CPK of 11,000 only four days later. The plan is to continue the treatment with close outpatient follow-up.

## 4. Narrative Review

### 4.1. Epidemiology

Statins are one of the most widely prescribed classes of medications, with more than 32 million people in the United States receiving statin therapy [1]. Muscular adverse effects are commonly associated with statin use, with 10 to 25 percent of all patients treated in clinical practice experiencing muscle-related symptoms ranging from mild myalgia to severe muscle weakness and rhabdomyolysis [2]. The most common of these side effects is lower extremity muscle cramping, which the majority of patients report as their primary reason for medication discontinuation [3]. Rhabdomyolysis is a less common adverse effect, with the incidence in patients on statin therapy varying from 1.6 to 6.5 per 100,000 persons per year with a case fatality of 10% [4]. Rarely, patients taking statins may experience an immune-mediated necrotizing myopathy (IMNM). Though the incidence of IMNM is only 2 to 3 per 100,000 persons receiving statin therapy, it represents a large number of people due to the vast amount of patients being treated with statin therapy in the United States [5].

### 4.2. History of IMNM Classification

IMNM as a clinical entity separate from other types of necrotizing myopathies was first described in 2010 by a group of researchers from Johns Hopkins Myositis Center. The group detected a specific antibody that thereby defined a subgroup of patients with necrotizing myopathy of autoimmune origin [6]. In 2011, the same group conducted a longitudinal study of patients with suspected myositis that ultimately identified the major antibody target as a 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGR) [7]. This study, which enrolled a total of 750 patients, found that 45 of those patients were positive for the anti-HMGR antibody. In addition to the group at Johns Hopkins, the European Neuromuscular Centre (ENMC) criteria also recognized anti-HMGR myopathy as a distinct clinical entity and a subtype of immune-mediated necrotizing myopathy along with autoantibody-negative IMNM and anti-signal recognition particle (anti-SRP) myopathy in 2016 [8]. In a study including data from The South Australian Myositis Database (SAMD), sera from 207 patients with idiopathic inflammatory myositis tested positive for anti-HMGR antibodies in 19 cases (9.2%). In comparison, sera from 151 people of a general reference population from the same area was positive for anti-HMGR antibodies in 0% of cases [9]. One New Zealand study conducted at Canterbury Health Laboratories in 2014 tested 425 patients with myositis for the anti-HMGR antibody. Only 13 patients tested positive for the anti-HMGR antibody, and 8 of the 13 were subsequently diagnosed with anti-HMGR IMNM.

### 4.3. Statin Exposure in Pathogenesis, and Statin Types Involvement

Because HMGCR is the target of statin medications, IMNM is commonly associated with exposure to statin therapy. Statins also upregulate HMGCR in regenerating muscle tissue, which may explain why the myopathy persists even after statin discontinuation [7]. The 2010 study at Johns Hopkins assessed anti-HMGCR autoantibodies with statin exposure prevalence to be 89% [6]. In their following study in 2011, the research group from the same institution reported 92% statin exposure in patients 50 years and older with anti-HMGCR IMNM and 67% 139 statin exposure in all antibody-positive patients [7]. In one study of 50 American patients with anti-HMGCR IMNM, statin exposure was found to be a significant factor in the development of the disease (OR=32.9,  $p < 0.001$ ), with 75% of antibody-positive patients having statin exposure. Strong association between anti-HMGCR antibodies and statin exposure was demonstrated in Australian study with sensitivity and specificity for anti-HMGCR antibodies by statin use was 0.94 and 0.78 respectively, with an extremely high negative predictive value for anti-HMGCR antibodies by statin use [9-10]. In contrast, a different study of 49 American patients with anti-HMGCR IMNM found a statin exposure prevalence of 2014 found statin exposure within a cohort of 45 patients with anti-HMGCR IMNM to be 44.4% ( $n = 20/45$ ), interestingly study also showed statin-exposed patients to be older than the antibody-positive, statin-naïve patients ( $p = 0.001$ ) [11]. According to the search in PubMed online library comparing different statins in light of relative risk of statin-induced IMNM development has not yet been studied extensively. There is only one published study defined atorvastatin as a predictor for development of the pathology. It is a case-control study with 69 patients taking statins, with multiple regression analysis revealed atorvastatin as a significant independent predictor of anti-HMGCR IMNM (OR 3.8,  $p=0.023$ ) [12]. In other published studies, the wide use of atorvastatin, simvastatin, pravastatin and rosuvastatin was demonstrated. We tried to find out which statin types are mostly involved in the development of pathology according to already published data. The Canterbury Health Laboratories study in New Zealand found the yearly incidence of anti-HMGCR IMNM to be 1 in 90,000 New Zealand statin users or 1.7 million people per year [13]. In this study out of 9 patients included in case series 4 were exposed to atorvastatin in the past and 162 two more patients were statin-I with atorvastatin comprises 57.2% of all lipid-lowering prescriptions in the country 164 [14]. In another study conducted in two neuromuscular centers in Boston, 21 out of 25 patients with IMNM and exposure to statins received atorvastatin, and 4 patients were exposed to simvastatin or pravastatin [15]. But according to the most recent published data atorvastatin comprises only 20.2% of all cholesterol-lowering medications or 22.7% from combined simvastatin, atorvastatin, pravastatin, rosuvastatin, lovastatin [16]. The study involved patients from STA-

TIN-PHESEMA showed that 84% of all the patients developed IMNM received atorvastatin [17]. The following observation is in a strict contrast with the most recent date about statin market share of prescriptions in one of the neighbor Canada provinces, where atorvastatin prescriptions comprise only 39% of all the statins prescribed [18]. In small Australian study including only 6 patients with statin-induced IMNM all patients were taking Atorvastatin [19]. Half of the French Myositis Network study's patients was exposed to atorvastatin, which is in accordance with statin prescription data in France, where around 40% 176 off all the statin prescriptions are made for atorvastatin [20]. Although the development of anti-HMGCR antibodies was initially described in connection to statin exposure, more recent studies have revealed cases of statin-naïve patients who are anti-HMGCR antibody positive. In one study of a pediatric population with juvenile myositis, 5 out of 440 total patients (1.1%) were positive for anti-HMGCR antibodies without any history of statin use. Among the 5 antibody-positive patients, 2 were diagnosed with IMNM and the remaining 3 were diagnosed with either JDM or JCTM [21]. One study in Hoboken pooled 2039 adult myositis patients and found that 75 of them (4%) were anti-HMGCR-positive without previous statin use [21]. In a study conducted in Japan among 33 patients with anti-HMGCR IMNM, only 7 patients (21%) were statin-exposed [22]. Differences in the 185 data obtained from Asian studies may be partially explained by the high popularity of oyster mushrooms, red rice yeast or pu-erh tea in Asian cuisine. These products contain high amounts of naturally produced 188 lovastatin, with up to 2.8% of the mass of the red rice yeast comprised of lovastatin [22].

### 5. Laboratory Studies

The production of antibodies in predisposed patients is most likely activated by an increase of the HMGCR with statin exposure [4]. In vitro studies showed impaired muscle regeneration with presence of anti-SRP and anti-HMGCR antibodies [23]. It was shown that HMGCR shares regions of homology with human papillomavirus type 58, which suggests a link between infection and activation of the autoimmune process [24]. For the diagnosis of anti-HMGCR necrotizing myopathy, elevated creatine kinase levels accompanied by proximal muscle weakness and positive anti-HMGCR antibodies is sufficient to make the diagnosis [25]. Although level of CK does not accurately reflect disease activity, it is used in diagnosis of all myopathies. The median peak CK is around 4700 IU/L in patients with anti-HMGCR myositis [24]. There was an association between levels of CK and anti-HMGCR titers independently of the time elapsed from the beginning, age at disease onset, sex, race or immunosuppressants treatment [26, 27]. Class II HLA DRB1\*11:01 allele is strongly associated with anti-HMGCR myositis, with an odds ratio of 24.5 in Caucasians and 56.5 in African Americans [28]. In another study with only 205 19 patients positive for anti-HMGCR antibodies, the odds ratio was 56 even after adjusting for 206 gender and statin use [9]. PPV

for patients positive for HLA-DRB1\*11:01 was 42% with 207 increase up to 90% in patients also exposed to statins [9]. In the study of 440 pediatric patients with juvenile myositis, not one patient had the DRB1\*11:01 allele. However, 208 the DRB1\*07:01-209 DQA1\*02:01 haplotype was present in 4 anti-HMGCR-positive pediatric patients ( $p=0.0035$  in 210 comparison with control group) [21]. In one study investigating the association of HLA I and II antigens among HMGCR-positive patients with mild statin intolerance, it was found that the DRB1\*11:01 allele is associated with statin intolerance in Caucasians and African-Americans [29]. Caucasian anti-HMGCR patients had a higher frequency of the combination DR11; DQA5; DQB7 than the control population (70% vs 17%). This was not demonstrated for African American anti-HMGCR patients (13% vs 3%). However, there was a prominent increase in frequency of DR11 in African American patients positive for anti-HMGCR antibodies compared to controls (88 vs 21%). 95% of patients with DR11 in this study were positive for the DRB1\*11:01 allele. Additionally, it was found that DQA1 and DQB6 were less frequent in Caucasian anti-HMGCR positive patients compared to controls (25% vs 64%). According to this data, almost 10% of the patient population being DR11-positive and DR11-negative rarely develop anti-HMGCR autoantibodies [9]. HLA determination could be an important step in the diagnosis of the condition. Different results were obtained in the study conducted in Japan [22] including 40 anti-HMGCR patients with IMNM. DRB1\*11:01 was more prevalent in patients with anti-HMGCR autoantibodies than in patients with other forms of IMNM ( $p=0.0073$ ), although patients from Japan demonstrated high prevalence of DRB1\*08:03 ( $p=0.00016$ ). The cause is more likely to be related to a high prevalence of DRB1\*08:03 in Japanese population (7.7% vs. 0.2% in European Americans). Of interest, DRB1\*11:01 is only half as prevalent in Japanese population as it is in European Americans (2.5% vs. 5.6%) [22].

## 6. Muscle Biopsy

In patients with IMNM, the pathological findings most often show necrosis with scarce inflammatory infiltrate. Very rarely, a pathologic picture of marked inflammation can be seen. In one study of 55 patients found to have anti-HMGCR antibodies, a muscle biopsy was performed in 53 of them [30]. In 38 patients (71.7%) the biopsy demonstrated predominantly necrotizing myopathy with minimal or no lymphocytic infiltrate. Prominent endomysial and/or perivascular inflammation with myofibers necrosis was demonstrated in 10 patients (18.9%). In 2 cases (3.8%) there was prominent myofiber necrosis with accompanied vacuoles. Two more patients (3.8%) showed inflammatory muscle biopsy results with minimal or absent myofiber necrosis. One subject (1.9%) had a normal muscle. These changes are in accordance with the findings of a small New Zealand study, where 7 patients underwent muscle biopsy. These biopsies demonstrated muscle necrosis, extensive macrophage infiltrate, and in some cases, muscle regener-

ation changes [13]. These same findings were also demonstrated in a small Australian study with 6 patients [19]. In another study including 24 specimens of muscle biopsy from anti-HMGCR positive patients, necrotizing myopathy was demonstrated in 23 cases. In 1 case, prominent endomysial and perivascular inflammation was seen [29]. In another study including 18 patients with anti-HMGCR, CD68+ was the most prominent cell type. These cells were found mostly in endomysial and perivascular areas. Another study from 2018 that analyzed immunopathological characteristics of biopsy samples from IMNM patients without statin exposure also found CD68+ macrophages within necrotic muscle fibers and endomysial muscle tissue [31]. Among macrophages, the type most often encountered was M2, which plays a role in muscle regeneration and repair. In this study, 19% of patients demonstrated M1 macrophages on the muscle biopsy. CD4+ and CD8+ cells in the endomysial region were found in 50% of patients, as well as in the other study conducted in Australia [9]. CD 20+ cells were found in only 17% of patients. Plasmacytoid dendritic cells (CD123+) were found 254 in endomysium and perivascular areas in 63% of patients. MHC class I complexes were up-regulated on the sarcolemma of muscle fibers in 88% of cases. Membrane attack complex (MAC) were found in 44% cases, mostly on endomysial capillaries and on the surface of non-necrotic muscle fibers. In contrast, MAC was also demonstrated in small perimysial blood vessels and surface of non-necrotic muscle fibers, but not in endomysial capillaries. Small perimysial blood vessels were stained for MAC in 75% of cases, and non-necrotic muscle fibers in 50% of cases [32, 9].

## 7. MRI

In one study including 666 patients with different types of myopathies (dermatomyositis, polymyositis, clinically amyopathic dermatomyositis, inclusion body myositis, and immune mediated necrotizing myopathy), MRI was studied as a tool for differential diagnosis [26]. 50 patients with anti-HMGCR myopathy showed less severe muscle involvement than patients with anti-SRP myopathy. Muscle abnormalities were most significant in the lateral rotator and gluteal groups (especially adductor brevis edema and obturator externus atrophy). Compared with DM or PM, IMNM was characterized by a higher proportion of thigh muscle edema (56% vs. 30%), atrophy (23%) and fatty replacement (38%). Patients with IMNM demonstrated early fatty replacement of the muscle tissue. Despite the named differences, this study concluded that MRI does not adequately discern between different types of myopathies, having only a 55% positive predictive value for diagnosing IMNM. However, the negative predictive value for IMNM was high at 93.1% [26].

## 8. Management of IMNM

Currently, no clinical guidelines exist to guide the management of patients with IMNM. Current recommendations are based only

on data extrapolated from case reports, observational studies, and personal experience. However, the ENCM does recommend that treatment begin with a combination of corticosteroids and methotrexate [33]. Other immunosuppressive therapies may also be used if a patient is intolerant to methotrexate or corticosteroids. These include alternatives such as azathioprine, mycophenolate, tacrolimus, cyclosporine, or cyclophosphamide. These therapies have been demonstrated to be effective on an individual basis in multiple studies [19]. IVIG has also demonstrated high efficiency and tolerability as a first-line agent in small set of patients who refused steroids as medication of the first-line [21].

## 9. Prognosis

Not enough studies done yet to assess prognosis in patients with statin-induced IMNM. One study involved 50 patients who were followed for more than 2 years showed that only 44% were able to regain full strength with the use of physical therapy. Of the 50 patients, 55% maintained CK levels greater than 500 IU/L. Only 3 patients could be weaned off immunosuppressive therapy completely. Younger patients had more prominent weakness and older patients had a faster rate of strength recovery independent of sex, race, time from disease onset, and treatments received [26].

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