

Persistent Liver Enzyme Abnormalities Precedes Proximal Muscle Weakness: A Rare Case Report of Anti-HMGCR Necrotizing Myopathy in a Statin Naive Female

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Abstract

Within the past decade, a novel antibody to HMG-CoA-Reductase [3-hydroxy-3-methylglutaryl coenzyme A reductase] has surfaced as the possible link to statin associated Necrotizing Autoimmune Myopathy (NAM). This antibody, however, has now also been discovered in NAM without prior statin exposure sparking heightened interest in the pathophysiology. This case reports highlights a unique initial presentation of this obscure disease process to promote clinical awareness and discuss potential novel mechanisms leading to the development of Anti-HMGCR autoimmune necrotizing myopathy. Future research attempts should continue to identify additional genetic and phenotypic risk factors in predisposed individuals to facilitate early diagnosis of this disease process to prevent unnecessary functional decline.

Keywords

obscure disease; muscle weakness; liver enzyme; necrotizing autoimmune myopathy

Introduction

Necrotizing Autoimmune Myopathy (NAM) is an uncommon disorder often confused with Polymyositis given the symptoms of proximal muscle weakness at clinical presentation. Paraneoplastic syndromes and statin use have historically been associated with NAM [1,2]. Recent expanding research efforts have focused on revealing the pathogenesis of this obscure disease process. Statins are potent inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR) and this enzyme plays an important role in cholesterol synthesis within liver cells [3]. Within the last decade a novel autoantibody to this protein has been discovered in individuals with statin associated NAM [4]. This antibody, however, has now also been discovered in NAM without prior statin exposure sparking heightened interest in the pathophysiology driving Anti-HMGCR autoimmune necrotizing myopathy. Despite the abundance of this enzyme within liver cells as well as muscle, associated abnormalities in liver enzymes in these patient populations have never been previously described.

This case report highlights a unique initial presentation of this obscure disease process to promote clinical awareness and discuss potential novel mechanisms leading to the development of Anti-HMGCR autoimmune necrotizing myopathy. It also illustrates the need for more research trying to further

identify genetic and phenotypic risk factors predisposing statin naïve individuals to developing anti-HMGCR myopathy in order to prevent unnecessary functional decline in the setting of delayed diagnosis.

Case Report

A 56 year old African American female patient with a past medical history of hypertension presented to the emergency department (ED) January 2015 with a chief complaint of fatigue and general malaise. Work up at the time showed isolated liver enzyme abnormalities thought to be secondary to an underlying viral infection. Her constitutional symptoms resolved, but isolated liver enzyme elevations persisted. She was followed as an outpatient with extensive hepatic work up, including biopsy, which was negative for any particular etiology and no treatment was implemented despite persisting enzyme abnormalities.

May 2015, five months following her initial presentation described above, she presented to the ED with new progressive proximal upper and lower extremity muscle weakness and myalgias. Tenderness of proximal hip/gluteal muscles and 4/5 muscle strength in bilateral hip flexors and 4+/5 bilateral shoulder abduction was noted on physical examination. Muscle strength was 5/5 in the remaining bilateral upper and lower extremities. Laboratory workup revealed significantly elevated creatinine kinase (CK) levels [8600 IU/L], lactate dehydrogenase (LDH) [738 IU/L], Aldolase [>56.0 IU/L], and aspartate aminotransferase and alanine aminotransferase (ALT/AST) [281/188 IU/L]. Lower extremity magnetic resonance imaging (MRI) revealed proximal hip and gluteal muscle edema [Figure1]. Subsequent Electromyography and Nerve Conduction Velocity [EMG/NCV] studies confirmed an underlying myopathic process. Left vastus lateralis muscle biopsy showed multifocal necrotic fibers with minimal inflammatory cells confirming the diagnosis of a necrotizing myopathy [Figure1]. A paraneoplastic workup was negative, including CT chest/abdomen/pelvis, and her breast and colon cancer age appropriate screening were up to date. Anti-HMGCR antibodies were positive despite lack of prior statin exposure consistent with an autoimmune myopathy. Pulse dose 1 gram intravenous (IV) Solumedrol was given for five days during her acute hospitalization as initial treatment along with a single intravenous Immunoglobulin (IVIG) infusion of 24g. Improvements were noted in CK levels prior to discharge and she was continued on high dose oral prednisone 60mg and set up for serial outpatient IVIG infusions.

During the subsequent six month follow up period, IVIG was continued every three weeks and oral prednisone was tapered from 60 milligrams (mg) to 5mg with a symptomatic flare of myalgias and weakness with an associated increase in CK noted when reaching 5mg requiring a prolonged taper at 10mg [Figure 2]. She eventually tapered off oral steroid therapy with IVIG monotherapy in August 2015, but within two months, she developed significant myalgias prompting hospitalization requiring pulse dose Solumedrol 1g IV infusion for three days with concurrent IVIG over two days. Of note, there was no significant increase in her CK levels during this "acute" flare and additional autoimmune workup was entirely negative [Anti-DNA Abs, Anti-Smith/Scl-70/Histone/Jo-1, ANA, SSA/SSB, Anti-RNP].

Subsequent outpatient follow up showed stable elevations of CK [1692] with subjective reports of worsening myalgias. HMGCAR Antibodies were resent and were positive showing no detectable decrement in antibody levels. She continues with IVIG infusions every three weeks with serial CK monitoring. Although steroid sparing agents have been discussed in treatment of this pathologic process, these agents have not been explored in treatment for this patient.

Discussion

NAM mimics other inflammatory myopathies at symptom onset, but it is distinguished by the paucity of inflammatory cells on muscle biopsy with notable fiber necrosis and regenerating muscle fibers [8]. Like many other necrotizing myopathies, the mechanism of muscle cell death remains to be elucidated. The exact overall prevalence has been difficult to discern, but it has been observed in statin therapy, cancer or rheumatologic conditions, post-viral syndrome and idiopathically [9]. In fact, Kassardian et al just recently examined the phenotypic features of 63 patients with NAM [clinical, serologic, and electrophysiologic] corroborating this clinical observation and dividing patients into four categories of NAM [1] idiopathic: no risk factor identified, [2] statin associated: receiving statin medication at symptom onset; [3] paraneoplastic: cancer identified within two years of myopathy onset; and [4] connective tissue disease associated: connective tissue disease known or diagnosed after myopathy [10].

Statins are potent inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR) and one of the most commonly prescribed medications in the United States [2]. Albeit statins have a good safety profile, certain side effects limit their use in 5-20% of patients, namely statin-associated musculoskeletal side effects. In most cases, these side effects are self-limited after discontinuation of statin therapy; however, a study recently performed by Amata et al noted a small subgroup of patients with refractory symptoms despite discontinuation of statins. These patients were responsive to immunosuppressive therapies. Given the lack of response after discontinuing statins and improvement with immunosuppression, an immune-mediated phenomenon was hypothesized as the driving factor for refractory symptoms [1]. Subsequent research performed by Mammen et al analyzed a large cohort of 225 patients with biopsy proven necrotizing myopathy with proximal muscle weakness and identified 26 individuals with a novel autoantibody to HMGCR [4]. This discovery strengthened the theory of a novel autoimmune process driving refractory statin myopathy despite discontinuation of therapy.

Anti-HMGCR NAM is a rare condition with an estimated incidence of 2 per million per year in the US and research has revealed a small subset of these patients lack previous statin exposure [7]. This research has prompted additional European studies in patients with known NAM and a majority of the patients who had anti-HMGCR positive myopathy, albeit still rare in occurrence, were statin naïve [6]. In France, studies looking at the correlation between anti-HMGCR myopathy and statin use found 56% of patients were statin naïve [6]. In contrast, a recent epidemiological study in Prague observed the incidence of NAM over a ten year period from 2004 - 2014, and of the 233 patients diagnosed with any form of biopsy proven inflammatory myopathy, none of the patients in this study who were positive for anti-HMGCR autoantibodies were statin naïve [13]. Studies performed in the United States estimate roughly 27% are statin naïve and there are no significant differences in gender, EMG and MRI findings, prevalence of weakness, or HLA predisposition when looking between statin exposed vs naïve patients [7]. Phenotypic analysis has shown a higher prevalence of statin naïve patients tend be younger (37 +/- 17 vs 59 +/- 9), include more African Americans [53% vs 13%] and have higher average peak CK levels [13,392 +/- 8839 vs 7881 +/- 5875] [7].

Genetic studies suggest HLA-DR11, -DQA5, and -DQB7, are more prevalent among individuals diagnosed with anti-HMGCR myopathy in Caucasian populations, but only DR11 was associated strongly

with anti-HMGCR myopathy in African Americans. HLA-DR11, therefore, overlaps both Caucasian and African American races, and specifically the DRB*11:01 allele which was present in 95% of these populations [12]. This allele, unfortunately, was not shown to be different when comparing statin-naïve versus statin-exposed patients. These results highlight the importance of additional research looking at genetic and phenotypic data to identify at risk individuals.

Why is understanding statin exposure important for patients diagnosed with anti-HMGCR autoimmune myopathy? Werner et al. observed 12 statin-exposed vs 5 statin-naïve patients with anti-HMGCR myopathy over a 2 year period treated with immunosuppressive agents and analyzed evolution of antibody levels, CK levels, and muscle strength. Statin-exposed patients had decreased antibody and CK levels and improved strength with immunosuppressive treatment over the two year period in comparison to statin-naïve patients who made no functional or serological evidence of improvement despite aggressive immunosuppressive treatments [14]. Despite the small sample size of this study, it suggests a possible prognostic role statin exposure may play when discussing disease course and treatment with these patients. This case shares similar serologic trends of statin-naïve patients in regards to refractory Anti-HMGCR antibody levels with stably elevated CK, and she still currently endorses myopathic symptoms.

A variety of immunosuppressive treatment strategies have been utilized for Anti-HMGCR myopathy. Patients are highly susceptible to relapsing symptoms when steroids are tapered and success often relies on prolonged multi-agent treatment with steroids and intravenous immunoglobulins (IVIg) or other immunosuppressive drugs [15]. It has been shown that anti-HMGCR antibody levels correlate with muscle strength and CK levels, but it remains to be investigated whether serial tracking of antibody titers would be of clinical benefit for monitoring patient improvement and determining treatment duration of immunosuppression [14].

Although the exact mechanism of anti-HMGCR myopathy is yet to be determined, the HMGCR protein is the target of an autoimmune response in certain predisposed individuals. It is hypothesized that treatment difficulties may be the direct consequence of the environmental up-regulation of HMGCR in regenerating muscle fibers which drives the autoimmune process [5]. Despite the abundance of HMGCR in liver cells, liver enzyme abnormalities have not been previously described in patients diagnosed with anti-HMGCR myopathy, independent of statin exposure. Why ALT/AST resolved, but CK levels still remain persistently elevated despite aggressive treatments in this patient is unexplained. Consideration should be taken in conservatively tracking liver enzyme abnormalities during treatment in patients diagnosed with myopathy in lieu of performing possible invasive procedures which may expose them to unnecessary complications.

Conclusion

This case report highlights a unique clinical presentation of autoimmune necrotizing myopathy associated with anti-HMGCR antibodies. Although statin exposure is associated with liver damage and anti-HMGCR myopathy, there is a growing body of literature indicating statin exposure is not a prerequisite for development of these antibodies and other unidentified factors seem to play a role. Future research attempts should continue to identify additional genetic and phenotypic risk factors in predisposed individuals to facilitate early diagnosis to prevent unnecessary functional decline.

Figures

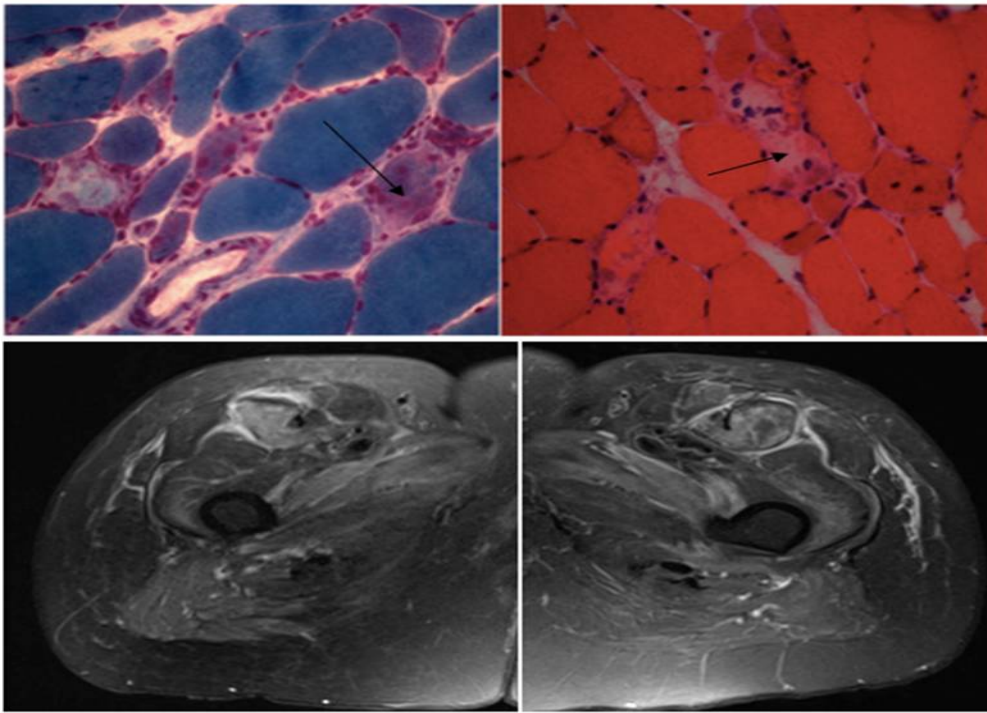


Figure 1: Modified Trichrome staining (top left) and H&E* staining (top right) of the left vastus lateralis muscle revealed scattered necrotic fibers (arrows) undergoing phagocytosis. Intramuscular blood vessels were normal without perivascular or perimysial inflammation. Multifocal necrotic fibers, associated inflammation and fiber regeneration were consistent with a necrotizing autoimmune mediated myopathy. T2-weighted Magnetic Resonance Imaging of bilateral femurs (bottom) revealed extensive symmetric edema involving gluteal, adductors, iliacus, posterior compartment musculature consistent with myositis. [*Hemotoxylin & Eosin]

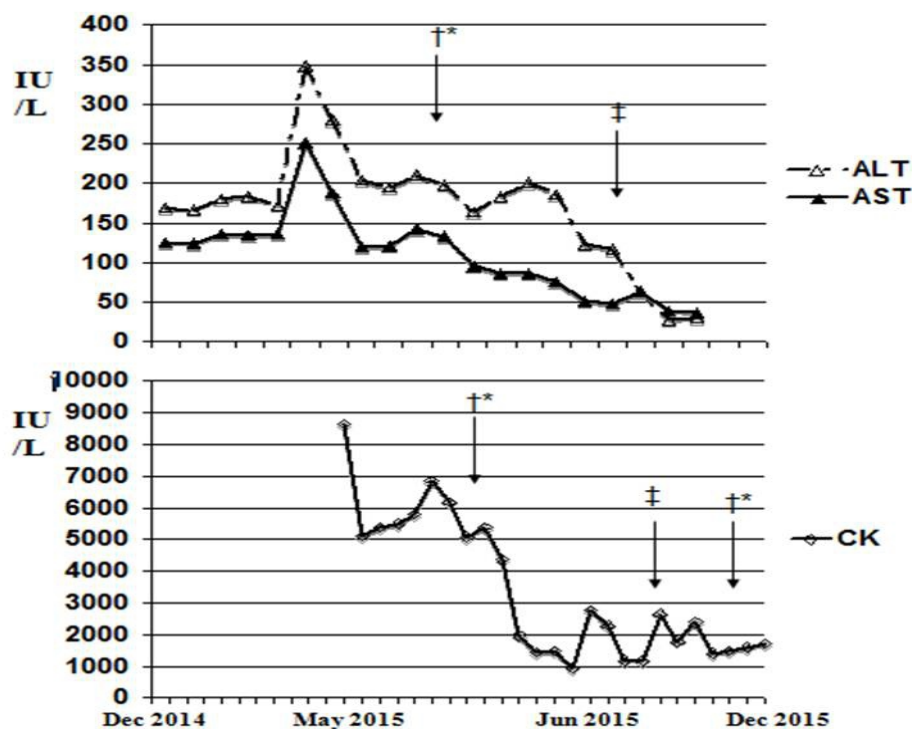


Figure 2: Immunosuppressive treatments improved Creatinine Kinase [CK] and Liver Transaminase [ALT/AST] levels concurrently. Intravenous Immunoglobulin [IVIG] was continued every three weeks at all times during time course described above irrespective of oral steroid therapy dosing. While ALT/AST [31/36] elevations resolved during treatment, CK levels still remain elevated [1692] requiring ongoing IVIG treatment.

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