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CASE REPORT

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Statin-induced necrotizing autoimmune myopathy: an extremely rare adverse effect from statin use

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ABSTRACT

Statins are widely prescribed medications to prevent cardiovascular events. While self-limited statin myopathy is relatively common, statin-induced necrotizing autoimmune myopathy (SINAM) is extremely uncommon, with incidence of two cases per million per year. We present a case of SINAM after a decade of atorvastatin use, leading to debilitating weakness. A 71-year-old male presented with recurrent falls due to extreme bilateral lower-extremity weakness without pain or sensory changes. No fever, chills, rash, joint pain, recent infection or medication changes were reported. Reported taking atorvastatin 80 mg daily for 10 years. Physical examination revealed significant muscle wasting on right deltoid and proximal muscle weakness in all extremities. Lab tests included elevated creatinine kinase, aldolase, ESR, CRP and transaminases. Anti-HMGCR antibody was significantly elevated. TSH, serum protein electrophoresis and RPR were unremarkable. ANA, Anti-Jo-1, anti-Mi2, anti-SRP, anti-ds-DNA, anti-SSA and anti-SSB antibodies were negative. MRI of thigh revealed diffuse myositis. Electromyogram revealed an acute myopathic process. Muscle biopsy showed muscle necrosis and C5b-9 sarcolemmal deposits on non-necrotic fibers without rimmed vacuoles. He was diagnosed with SINAM. Statin was discontinued, and steroid, immunoglobulins and azathioprine were started with gradual improvement. Unlike the self-limiting statin myopathy, SINAM is more severe and is associated with significant proximal muscle weakness, markedly elevated CK and persistent symptoms despite statin discontinuation. Anti-HMGCR antibodies are present in 100% of cases. Immunosuppressants are the mainstay of treatment, and statin rechallenge should never be done in these cases. Although relatively rare, physicians should be cognizant of SINAM.

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1. Introduction

Statins are a group of drugs that reduce the levels of triglyceride and cholesterol in blood by inhibiting HMG-CoA reductase, an enzyme involved in rate-limiting step in cholesterol synthesis. Statins are widely prescribed medications to prevent primary cardiovascular events and secondary prevention of myocardial infarction and stroke in patients with known coronary artery disease (CAD) [1]. Stain-induced myalgia and myopathy is a well-known adverse effect of the medication which prompts physicians to discontinue the medication and re-challenge with a different statin when symptoms subside. Unlike the commonly encountered statin-induced myopathy, statin-induced necrotizing autoimmune myopathy (SINAM) is a rarer and much severe form of statin myopathy which can lead to debilitating weakness requiring immunosuppressive therapy.

2. Case presentation

A 71-year-old male with a history of hypertension, diabetes mellitus, hyperlipidemia and CAD status post three-vessel coronary artery bypass graft in 2009 presented to our emergency department with a history of recurrent falls due to extreme bilateral lower-extremity weakness. Following revision surgery and removal of infected right knee prosthesis, he developed gradually progressive non-fatigable weakness over a period of 6–8 weeks. He had difficulty getting up from the seated position and lifting his feet off the floor but denied any muscle pain, cramps, fasciculation or sensory changes in his extremities. He denied any preceding fever, chills, rash, joint pain, dysphagia, diplopia, sialorrhea, recent systemic infection or medication changes. He had no easy bruising or other features suggestive of excess glucocorticoid. He denied any prior thyroid, rheumatologic or neurological disorder. There was no family history of rheumatologic or genetic myopathies. His medications included amlodipine, aspirin, atovaquone, famotidine, metoprolol tartrate, tamsulosin and senna–docusate. He was taking atorvastatin 80 mg daily for over 10 years.

At presentation, his vital signs included heart rate of 76/min, blood pressure of 120/77 mmHg, temperature

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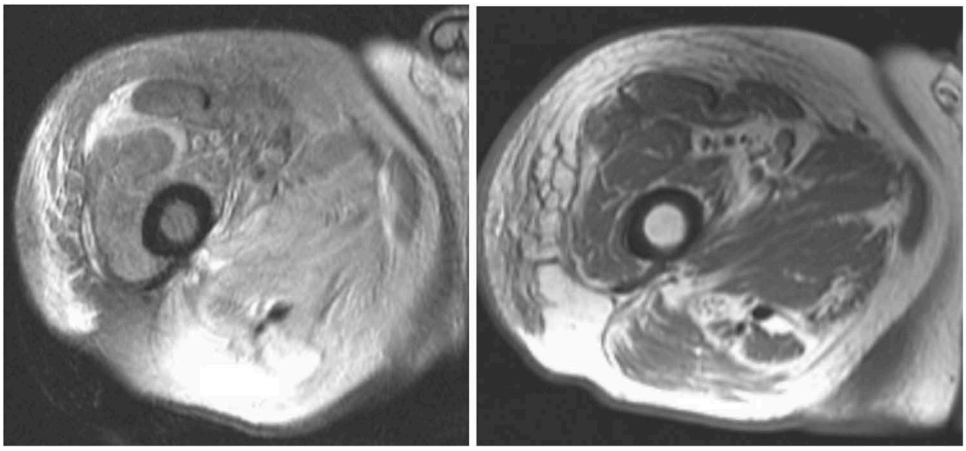

Figure 1 and 2. MRI of right thigh axial T1 & T2 with fat suppression showing extensive edema of the right thigh musculature, suggestive of diffuse myositis.

of 98.4°F and oxygen saturation of 98% in room air. On physical examination, he appeared tired but was not toxic appearing. He was noted to have mild temporal wasting and dry mucous membranes. He had marked atrophy of the right forearm, biceps and right thenar muscle. He had decreased muscle tone in his right upper extremity. The power in his bilateral proximal lower extremities was 3/5, that in bilateral proximal upper extremities was 4/5 and that in both upper and lower distal extremities was 5/5. Deep tendon reflexes were normal. He was also noted to have flexion contracture in the right elbow, with tenderness at the distal biceps tendon when trying to fully extend the right elbow actively or passively. The rest of the physical examination was otherwise unremarkable.

Lab tests revealed normal complete blood count, normal serum calcium level but low magnesium at 1 mg/dL which was appropriately repleted. Serum vitamin B12 was low at 154 pg/mL for which vitamin B12 supplementation was initiated. Other pertinent lab tests included creatine kinase 3334 IU/L (Ref: 30–223 IU/L), aldolase 24.7 U/L (Ref: 1.5–8.1 U/L), sedimentation rate 28 mm/h (Ref: 0–15 mm/h) and C-reactive protein 1.42 mg/dL (Ref: <1 mg/dL). 25-OH-vitamin D level was 30 ng/mL (Ref: 20–50 ng/dL) and TSH was 1.784 (Ref: 0.4–4 mIU/L). Liver transaminases were elevated – AST (226 IU/L; Ref: 13–39 IU/L) and ALT (62 IU/L; Ref: 7–52 IU/L). Anti-HCV antibody, serum protein electrophoresis and rapid plasma reagin were unremarkable. Antibodies including ANA, Anti-Jo-1, anti-Mi2, anti-SRP, anti-ds-DNA, anti-SSA and anti-SSB were negative. Anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (anti-HMGCR) antibody was significantly elevated at >200 U (Ref: 0–19 U). HLA or genetic study was not done.

MRI of thigh revealed extensive edema throughout the vastus lateralis muscle and proximal rectus femoris muscle, suggestive of a diffuse myositis(Figure 1 and 2). MRI of shoulder revealed post-surgical changes without acute tears or processes. MRI of cervical, thoracic and lumbar vertebrae revealed mostly degenerative changes and some cord compression but no acute findings. Electromyogram was done in 20 different muscles, and results were consistent with the acute myopathic process. Muscle biopsy showed muscle necrosis and C5b-9 sarcolemmal deposits on non-necrotic fibers without rimmed vacuoles.

He was diagnosed with SINAM. Statin was discontinued. The patient was started on Solumedrol 1000 mg IV for 3 days followed by Prednisone 60 mg daily. When HMGCA antibodies came back positive, he was started on IVIG 2 g/kg divided over 5-day course. At day 5 of IVIG therapy, there was no significant improvement and the patient was started on azathioprine 50 mg daily with a plan to administer IVIG chronically every 2 weeks and to titrate azithromycin dose to therapeutic. TMPT enzyme levels were checked and were within normal range. The patient was also started on oral Bactrim for pneumocystis prophylaxis. The steroid was slowly tapered over the course of weeks. Serum CK levels decreased to 195 IU/L within 2-week period and muscle weakness improved gradually. Muscle strength improved to 5/5 in all the affected muscle groups during subsequent follow-up in the neurology clinic.

3. Discussion

All the inflammatory myopathies share the common feature of immune-mediated muscle injury. The most common of these disorders are dermatomyositis (DM), polymyositis, overlap syndrome (with another systemic rheumatic disease), inclusion body myositis and immune-mediated necrotizing myopathy. Differentiating among the five types of inflammatory myopathies requires a stepwise approach including serum creatine kinase (CK) levels followed by EMG, followed by MRI and ultimately performing a muscle biopsy.

Necrotizing autoimmune myopathy (NAM) accounts for 19% of inflammatory myopathies [2]. Several causes including statin, paraneoplastic syndrome associated with lung, renal, breast and ovarian cancers, connective tissue disease and HIV infection have been associated with NAM [3]. SINAM is a relatively newly described and very rare adverse effect associated with the use of HMG-CoA reductase inhibitor. The estimated incidence of SINAM is two cases per million per year [4].

Statin-associated muscle toxicity includes a wide spectrum of manifestations from simple myalgia (characterized only by muscle pain) to myopathy and myositis (CK levels elevated more than 10 times the upper limit of normal). In most of these cases, symptoms subside when statin is discontinued (5).

The pathogenesis of SINAM is an area of active investigation. Studies have suggested that interaction between host immunogenetic background (specific class II HLA alleles, i.e.,, HLA-DRB1*11: 01 and 07: 01) and environmental triggers (statin or mushroom which is a natural source of statin) leads to multiple immune mechanisms ultimately converging on sustained autoimmune muscle injury and/or inadequate attempt at muscle regeneration [6]. Our case is unique as this rare side effect occurred after 10 years of statin use. Repeated infection of the hardware, revision surgery and physical therapy post-surgery might have played some role in triggering this event.

Unlike the self-limiting statin myopathy, SINAM is much more severe and is associated with significant symmetric proximal muscle (posterior thigh, medial thigh and gluteal compartments) weakness, markedly elevated CK level and persistent symptoms despite statin discontinuation [6]. It may rarely present with dysphagia, arthralgia or Raynaud's phenomena [7].

Nazir et al., in their systematic review of 100 cases, reported that assay (gold standard) has a specificity of ~94–100% and sensitivity of ~95–99% [8–10].

Muscle biopsy that is characterized by the presence of necrotic fibers without significant inflammatory cells, regenerating fibers and diffuse or focal upregulation of major histocompatibility complex 1 (MHC-1) may show increased sarcolemmal staining in non-necrotic fibers, and membrane attack complex immunostaining (e.g., C5b-9) may stain the sarcolemma with variable intensity as well as endothelial cells occasionally [11].

Once diagnosed, discontinuation of the offending agent and avoidance of this class of medication are the most important steps in the management of these patients [6]. Most patients show improvement after initiation of steroid, immunosuppressant and, in severe case, IVIG. Based on observational studies, the majority of patients required two or more immunosuppressants [12].

Therapeutic monitoring of patient with SINAM should include patient-reported functional changes and semi-quantitative muscle strength testing or quantitative dynamometry when available [6]. In addition, changes in serum CK levels can be used as a surrogate biomarker of disease activity [6]. Of note, some patients may have persistently elevated CK levels even when muscle strength is markedly improved or even normal [10]. Whether such patients warrant more aggressive therapy to decrease the CK levels and prevent chronic muscle damage remains unclear [6].

4. Conclusion

Anti-HMGCR antibodies are present in 100% of cases of SINAM. Immunosuppressants are the mainstay of treatment, and statin rechallenge should never be done in cases of SINAM. Although relatively rare, physicians should be cognizant of this entity and maintain a high index of suspicion in patients on statin presenting with myopathy, as early immunosuppressive therapy can significantly improve clinical outcomes.

Disclosure statement

No potential conflict of interest was reported by the authors.

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