Case Report

Statin-induced autoimmune necrotizing myopathy: A case report

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Abstract

Statin-induced autoimmune necrotizing myopathy is an extremely rare side effect associated with the treatment of statins. It is characterized by proximal muscle weakness, necrotizing myopathy and the presence of antibodies to HMG-CoA reductase. We report a case of a young female who was treated with atorvastatin and presented with progressive proximal muscle weakness with a very high creatine phosphokinase level, even after discontinuing atorvastatin. Muscle biopsy showed muscle necrosis with myophagocytosis. She showed a good response to treatment with oral prednisolone.

Keywords: Statin, Autoimmune, Myopathy, HMG CoA reductase, Creatine phosphokinase

Funding: None
Competing interest: None
Received: 10.08.2021 **Accepted revised version:** 22.11.2021 **Published:** 23.03.2022

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Cite this article as: Chamara R, Jayasinghe K. Statin-induced autoimmune necrotizing myopathy : A case report. Anuradhapura Medical Journal 2022; 16 (1): 18-20, DOI: http://doi.org/ 10.4038/amj.v16i1.7699

Introduction

Statins are used as lipid-lowering agents, which have shown a reduction in adverse cardiovascular events and mortality in patients with atherosclerotic cardiovascular disease. Although it is a relatively safe drug, it can rarely cause serious adverse events like rhabdomyolysis, hepatotoxicity, diabetes, and haemorrhagic strokes (1). Statin-induced autoimmune necrotizing myopathy (SIANM) is an extremely rare side effect with an incidence of 2 cases per million per year (2). It is characterized by the presence of autoantibodies against 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. Although muscle weakness may start soon after starting statins, it persists or may get worsen even after stopping the drug (3).

Case report

A 27-year-old female presented to National Hospital, Kandy with progressive weakness of limbs for four months. She was taking atorvastatin 10 mg nocte for two years for dyslipidaemia. After developing the muscle weakness, she had been initially seen by a physician at a peripheral hospital, and her creatine phosphokinase (CPK) was found to be elevated (3028 U/l), and atorvastatin had been discontinued. At this initial presentation, she had been unable to climb upstairs, but she had been able to walk on flat ground, and there had been no upper limb weakness.

Despite discontinuing atorvastatin, her weakness has worsened. When she presented to our hospital four months after stopping atorvastatin, she had marked muscle weakness. There was difficulty in standing up from the squatting position, difficulty in walking on flat ground and had difficulty in raising her arms.

On examination, her neck muscle power was 4/5. Upper limb proximal muscle power bilaterally was 3/5, and distally it was 4/5. In the lower limbs, muscle power was 2/5 proximally and 3/5 distally. Reflexes were normal in all four limbs. All the sensory modalities were intact. Other system examinations were unremarkable. The patient had markedly elevated CPK levels (30112 U/l). Alanine transaminase (ALT) was 289 U/l and aspartate transaminase (AST) was 309 U/l. Other liver function

tests, full blood count, urine full report, electrolytes, urea, creatinine, chest X-ray and electrocardiogram were normal. Erythrocyte sedimentation rate was 38 mm/h, and C reactive protein was 12 mg/l. Antinuclear antibody was positive, and titer was 1:100. Other autoimmune antibody screening was negative, including anti-double-stranded DNA (dsDNA), anti histidyl transfer RNA synthetase (JO1), anti-Sjögren's syndrome antigen A(RO), anti Sjögren syndrome antigen B (LA), anti-Smith (Sm), anti U1 small nuclear ribonucleoprotein (U1 NRP), anti-mitochondrial (AMA M2) and proliferating cell nuclear antigen (PCNA). Electromyogram showed evidence of chronic generalized myopathy mainly affecting proximal muscles. The nerve conduction test was normal.

Muscle biopsy showed several foci of necrosis and myophagocytosis with basophilic regenerating fibres and internalized nuclei. Perivascular inflammation and increase of endomysial connective tissue were not seen. Appearances were more in favour of chronic inflammatory myopathy.

Autoantibody for HMG-CoA reductase assay was not available.

After excluding other causes of myopathies, the diagnosis was made as SIANM.

Oral prednisolone was started with monitoring steroid side effects. She showed gradual improvement. Her CPK level came down (6410 U/l) but not to the normal range during the follow-up period of 6 months. Improvement of the weakness was noted, with mild residual weakness in the lower limbs. At six months of follow up, muscle power of her lower limbs was 4/5 proximally and 5/5 distally. The power of other muscle groups were 5/5.

Discussion

This case demonstrates that, although rare, SIANM is a side effect of statins that the physicians should be aware of, as statins are among commonly prescribed drugs. Moreover, withholding the culprit drug itself would not resolve the problem but need to be treated with specific treatments. Proximal muscle weakness with very high CPK levels in a patient who is taking a statin is suspicious of SIANM and can be confirmed by muscle biopsy if facilities for HMG-CoA reductase antibody assay are not available.

The incidence of SIANM is 2-3 cases per 100000 (4). It is characterized by the presence of muscle weakness, muscle necrosis and autoantibodies against HMG-CoA reductase (4). Pathogenesis of SIANM is believed due to this autoantibody acting on myocytes resulting in necrotizing myopathy (2).

This can occur as soon as commencing statins or many years afterwards. The dose of statins has no role in developing SIANM (3). The muscle weakness persists or can get worsen even after withholding statins (2). Although some statins like atorvastatin and simvastatin have a higher association with SIANM than rosuvastatin, there is no association reported between different statins (5). Our patient developed muscle weakness two years after commencing atorvastatin at a low dose.

She presented with progressive bilateral symmetrical proximal muscle weakness with elevated CPK. It is the most common presentation of SIANM. Extra muscular symptoms such as rash, arthritis, Raynaud's phenomenon, restrictive lung disease, cardiomyopathy, atrial tachyarrythmias, dysphagia, truncal muscle weakness and bulbar weakness have also been reported (2,3). A systematic review has shown that all the patients have presented with proximal muscle weakness, and 83.33% were symmetrical, and 92.8% were bilateral (2).

CPK levels are usually more than ten folds higher in idiopathic inflammatory myopathies (IIM) like dermatomyositis and polymyositis and could be even higher in SIANM (6). Mean CPK level was reported to be 6853 IU/l at initial presentation, which is 45 times of upper limit of normal (2). Our patient had even higher CPK levels at presentation (30112 IU/l), which is 200 times than normal.

Diagnosis is confirmed by detecting the antibodies against HMG-CoA reductase in serum. It is highly specific for SIANM. Sensitivity and specificity for detecting it are 94.4% and 99.3%, respectively (7). When there is no HMG-CoA antibody level available, diagnosis is made by the presence of necrotizing myopathy in the biopsy (2). Typical biopsy features are myofiber necrosis, less inflammation and lymphocytic infiltration and dominant macrophage population and an abundant myophagocytosis (8).

Treatments include discontinuing statins and starting oral prednisolone as initial therapy. Immunosuppressive drugs such as methotrexate, azathioprine, or mycophenolate mofetil can be included. Patients with severe weakness or resistance to combination therapy can be given intravenous immunoglobulin (IVIG) or rituximab (4). IVIG has been successfully used as a monotherapy in a patient with diabetes mellitus and can be used as initial therapy (9). Our patient showed good improvement with prednisolone alone even though she had severe symptoms. Immunosuppressive drugs can be tapered off once the patient has regained the full muscle strength (4).

Persistent elevation of CPK with normal muscle power suggests an attenuated but active disease process with a

greater rate of muscle regeneration. Persistent weakness with normal CPK suggests permanent muscle damage(4).

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