Statin-induced necrotizing autoimmune myopathy: importance of early recognition

Introduction

A 68-year-old woman treated with atorvastatin for 3 years following a myocardial infarction presented with gradual onset progressive weakness of the lower limbs and unsteady gait. Clinical assessment confirmed a severe proximal myopathy and her creatine kinase level was found to be markedly elevated. A biopsy of the quadriceps muscle demonstrated scattered necrotic and regenerating muscle fibres with no significant inflammatory infiltrates and deposition of membrane attack complex in keeping with the diagnosis of necrotizing autoimmune myopathy. Moreover, autoantibodies to 3-hydroxyl-3-methylglutaryl-coenzyme-A reductase (HMGCR) were detected in the serum. Treatment with high-dose corticosteroids resulted in complete recovery over a period of 6 months and normalization of muscle biomarkers.

Discussion

There is extensive evidence supporting the role of statins in primary and secondary prevention of cardiovascular events (Endo, 2010). Guidelines presented by the American College of Cardiology/American Heart Association Task Force reported that statins were the only cholesterol-lowering agent that had a mortality benefit (Stone et al, 2013). These guidelines expanded the statin-eligible population to 1 billion worldwide (Ioannidis, 2014).

Although statins are well tolerated, 5–10% of patients experience myalgia; other side effects include deranged liver enzymes and rhabdomyolysis (Thompson et al, 2016). Muscle damage secondary to statin use is caused by coenzyme Q10 depletion leading to mitochondrial dysfunction and myocyte apoptosis. This injury is reversible after withdrawal of statin, with recovery time of 2–3 months (Taylor et al, 2015). If muscle weakness persists with markedly raised creatine kinase levels despite discontinuation of drug, statin-induced necrotizing autoimmune myopathy should be suspected.

Statin-induced necrotizing autoimmune myopathy is rare, with an incidence of 2 per million per year. The pathophysiology of statin-induced necrotizing autoimmune myopathy involves upregulation of HMGCR in patients consuming statins, combined with major histocompatibility complex class 1 (MHC-1) expression for HMGCR antigens leading to production of anti-HMGCR antibodies, a sensitive diagnostic marker for statin-induced necrotizing autoimmune myopathy (Mohassel and Mammen, 2013). Muscle biopsy characteristically reveals necrotic muscle fibres with absent or minimal inflammatory infiltrates. Immunosuppressive therapy is the mainstay

Dr Arif Hussenbux, Core Medical Trainee, Department of General Medicine, Wexham Park Hospital, Wexham, Berkshire SL2 4HL

Dr Monika Hofer, Consultant Neuropathologist, Department of Neuropathology, Oxford University Hospital NHS Foundation Trust, Oxford

Dr Alan Steuer, Consultant Rheumatologist, Department of Rheumatology, Frimley Health NHS Foundation Trust, Oxford

Correspondence to: Dr A Hussenbux (arif.hussenbux@hotmail.co.uk)

CASE REPORT

A 68-year-old woman presented with an 8-month history of gradual, progressive weakness of the lower limbs. This culminated in several falls and an unsteady gait, especially while using stairs, which precipitated her admission to hospital. Her past medical history included a Dukes B adenocarcinoma of the bowel treated with an anterior resection 8 years earlier and a myocardial infarction requiring percutaneous coronary intervention and single stent insertion 4 years before admission. She commenced atorvastatin 40 mg following the percutaneous coronary intervention and remained on this until her admission to hospital. She reported no family history of neuromuscular or autoimmune diseases.

Physical examination confirmed significant proximal weakness of her lower limbs. Deep tendon reflexes were intact with no sensory deficit demonstrable. Laboratory studies confirmed a markedly raised creatine kinase level of 8296 units/litre (normal range 26–192 units/litre) and an elevated alanine transaminase level of 519 IU/litre (normal range <34 IU/litre). Subsequent computed tomography scan of the chest, abdomen and pelvis was normal, ruling out obvious malignant or paraneoplastic causes of her presentation.

Anti-nuclear antibody was positive with immunofluorescence demonstrating a fine speckled pattern; extractable nuclear antigen (ENA) screen including anti-Sm, nRNP, SSA(Ro), SSB(La), Jo1, PM-Scl, CL, PL4, Ku, Mi-2, PL-7, PL-12, SRP and Scl70 antibodies were not detected. Anti-3-hydroxyl-3-methylglutaryl-coenzyme-A reductase (anti-HMGCR) antibodies were present in serum.

The patient subsequently underwent biopsy of the left quadriceps. This demonstrated scattered fibres at various stages of necrosis or regeneration. Necrotic fibres were pale with myophagocytosis and regenerating fibres appeared basophilic with ground glass myonuclei. Immunohistochemistry reported strong upregulation for major histocompatibility complex 1 in necrotic fibres with relative sparing of the surrounding muscle fibres. There was C5b-9 (membrane attack complex) deposition on a small number of fibres and capillaries. The overall picture of scattered necrotic and regenerating fibres without significant inflammatory infiltrates was supportive of a statin-induced necrotizing autoimmune myopathy, also known as immune-mediated necrotizing myopathy (*Figure 1*).

Atorvastatin was stopped and the patient started treatment with prednisolone 60 mg. After several weeks the patient made a marked clinical improvement and was discharged from hospital. Her creatine kinase levels returned to normal and her prednisolone dose was reduced to 5 mg over a 12-month period without recurrent myopathy (*Figure 2*). Atorvastatin was discontinued and replaced with ezetimibe. She experienced no side effects and her lipid profile normalized.

Figure 1. **a.** Haematoxylin and eosin-stained frozen section of skeletal muscle cut transversely. Low power image showing scattered necrotic and regenerating fibres. Pale fibres are necrotic, those that are slightly purple (basophilic) are more likely to be regenerating. Some examples are circled. Note the relative lack of inflammation, hence the term necrotizing myopathy. **b.** Higher power image showing pale necrotic fibres. **c.** Major histocompatibility complex class 1 (MHC-1) immunostaining labels scattered fibres at various stages of necrosis and regeneration. Some non-necrotic fibres also show varying degrees of sarcolemmal staining, which may point towards an immune-mediated necrotizing process. **d.** C5b-9 (membrane attack complex) immunostaining shows complement deposition on scattered fibre with characteristic granular sarcolemmal staining; this is accompanied by complement deposition in the capillaries, suggestive of an immune-mediated necrotizing myopathy. Statin-related immune-mediated necrotizing myopathy typically shows 3-hydroxyl-3-methylglutaryl-coenzyme-A reductase (HMGCR) autoantibodies.

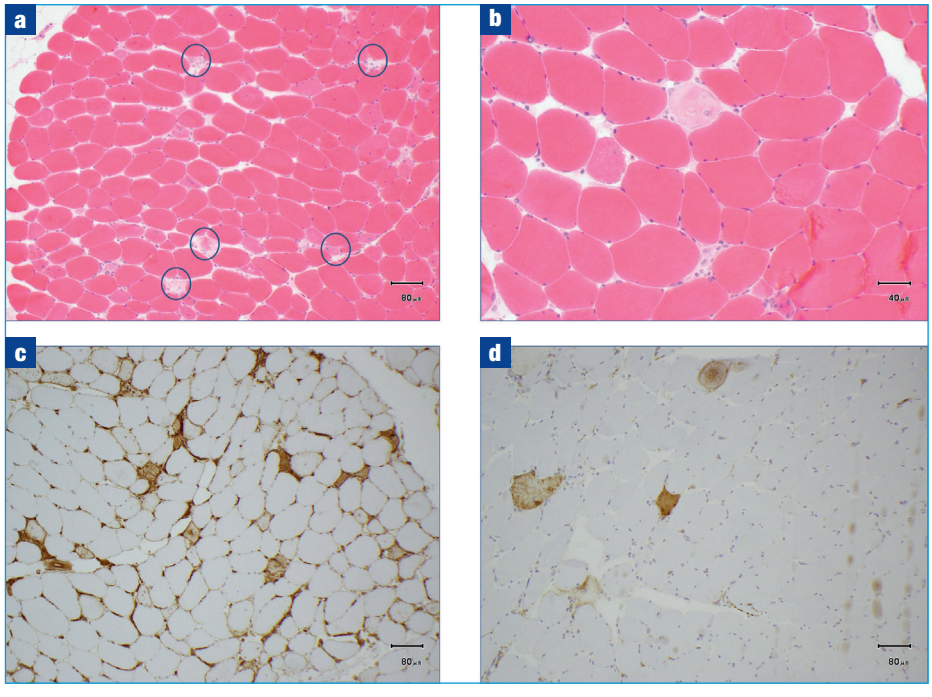
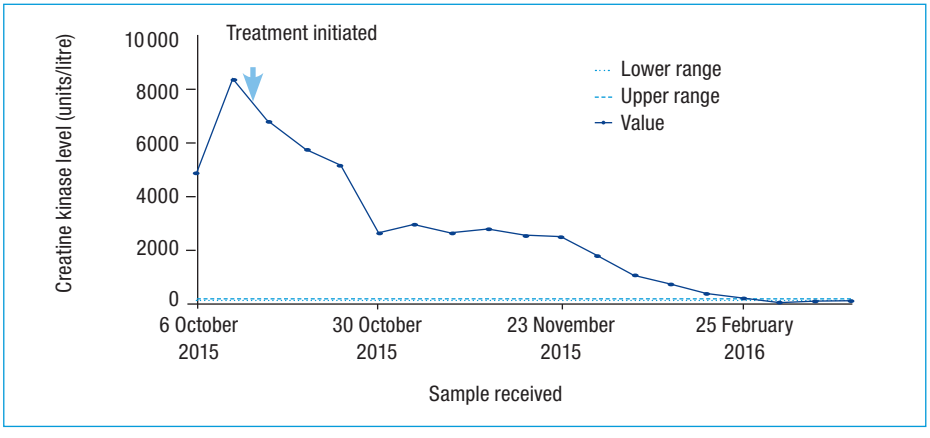


Figure 2. Creatine kinase fluctuations after commencing corticosteroid therapy.



of management, initially involving high dose prednisolone (1 mg/kg/day). Steroid-sparing agents include methotrexate (0.3 mg/kg/week for at least 2 years), azathioprine and mycophenolate mofetil. In severe cases intravenous immunoglobulin can be considered, and rituximab used for resistant disease (Ramanathan et al, 2015).

With the increase in statin use, statin-induced necrotizing autoimmune myopathy is an important consideration for general physicians in any patient with persistent muscle weakness and elevated creatine kinase levels despite discontinuing statin therapy. Workup in these cases involve electromyography, muscle biopsy and anti-HMGCR antibody testing. This patient had an excellent response to steroid therapy alone, highlighting the importance of prompt recognition (Kassardjian et al, 2015). **BJHM**

LEARNING POINTS

- Creatine kinase levels should be tested in all statin-treated patients presenting with myalgia and/or weakness.
- Statins can cause a severe but treatable autoimmune myopathy.
- Anti-3-hydroxyl-3-methylglutaryl-coenzyme-A reductase antibodies give a clue to the diagnosis. Further investigation involves electromyography and muscle biopsy.
- Statin-induced autoimmune myopathy has a negative autoimmune panel in serum with a lack of inflammatory infiltrate on muscle biopsy.
- Initial treatment involves high dose corticosteroids. Steroid-sparing agents such as methotrexate and intravenous immunoglobulin are reserved for severe cases.

Endo A (2010) A historical perspective on the discovery of statins. *Proc Jpn Acad Ser B Phys Biol Sci* **86**(5): 484–493. https://doi.org/10. 2183/pjab.86.484

Ioannidis JP (2014) More than a billion people taking statins?: Potential implications of the new cardiovascular guidelines. *JAMA* **311**(5): 463–464. https://doi.org/10.1001/jama.2013.284657

Kassardjian CD, Lennon VA, Alfugham NB, Mahler M, Milone M (2015) Clinical features and treatment outcomes of necrotizing autoimmune myopathy. *JAMA Neurol* **72**(9): 996–1003. https://doi.org/10.1001/jamaneurol.2015.1207

Mohassel P, Mammen AL (2013) Statin-associated autoimmune myopathy and anti-HMGCR autoantibodies. *Muscle Nerve* **48**(4): 477–483. https://doi.org/10.1002/mus.23854

Ramanathan S, Langguth D, Hardy TA et al (2015) Clinical course and treatment of anti-HMGCR antibody-associated necrotizing autoimmune myopathy. *Neurol Neuroimmunol Neuroinflamm* **2**(3): e96. https://doi.org/10.1212/NXI.0000000000000096

Stone NJ, Robinson JG, Lichtenstein AH et al (2013) ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. *Circulation* **129**(25 Suppl 2): S1–45. https://doi.org/10.1161/01.cir.0000437738.63853.7a

Taylor BA, Lorson L, White CM, Thompson PD (2015) A randomized trial of coenzyme Q10 in patients with confirmed statin myopathy. *Atherosclerosis* **238**(2): 329–335. https://doi.org/10.1016/j.atherosclerosis.2014.12.016

Thompson PD, Panza G, Zaleski A, Taylor B (2016) Statin-associated side effects. *J Am Coll Cardiol* **67**(20): 2395–2410. https://doi.org/10.1016/j.jacc.2016.02.071