Atorvastatin-associated necrotising inflammatory myopathy

Sirs,

Statin-treated patients may develop a non-inflammatory myopathy, however the spectrum of statin-associated muscle disorders is wider than we thought (1).

An 83-year-old woman developed fatigue, muscle aching, and weakness of shoulders, hips and thighs while taking atorvastatin (20 mg daily). Atorvastatin was started two years prior, at a stable dose, and she was not taking any other medications potentially associated with myopathy.

Proximal limb-girdle muscles were tender and weak, strength assessed at 2 to 3 of 5 bilaterally, deep-tendon reflexes + and symmetric, and plantar responses flexor; there were no fasciculations, cramps, skin rash, and pitting oedema.

Laboratory studies were normal except for myoglobin 1120 ng/ml (normal 50–110), creatine kinase 4457 U/L (20–200), aspartate aminotransferase 210 U/L (5–40), alanine aminotransferase 391 U/L (5–40), and lactate dehydrogenase 1455 U/L (210–400). An autoimmunity screening and a total-body computed tomography were unrevealing.

Atorvastatin was discontinued, though severe fatigue, muscle tenderness and weakness worsened; three weeks later she was unable to walk and enzyme levels were unchanged. T2-weighted sequences of a gadolinium-enhanced magnetic resonance imaging (MRI) showed a bright signal of thigh muscles, suggesting an infiltrative or inflammatory process with oedema (Fig. 1). A biopsy of the right quadriceps muscle disclosed muscle fiber necrosis, atrophy, an endomysial inflammatory infiltrate composed of $CD4^+$ (30%) and $CD8^+$ (70%) lymphocytes; major histocompatibility complex (MHC)-I was strongly expressed on muscle fibre surface.

Prednisone (2 mg/kg daily) at tapering doses was started, with noticeable improvement. One month later, while still on prednisone 0.75 mg/kg, the patient could walk and arise from a chair without difficulty, muscle enzymes returned to normal and a MRI of thighs showed muscle atrophy with no evidence of any infiltrative or inflammatory disorders.

Statin myopathy is a dose- and time-related non-inflammatory disorder characterised by fibre necrosis and atrophy with no inflammatory infiltrates (1). Muscle biopsy showed in our patient a necrotising polymyositis-like inflammatory myopathy with severe muscle fibre necrosis and atrophy and a prominent and diffuse inflammatory lymphoid infiltrate mainly composed of cytotoxic $CD8^+$ lymphocytes.

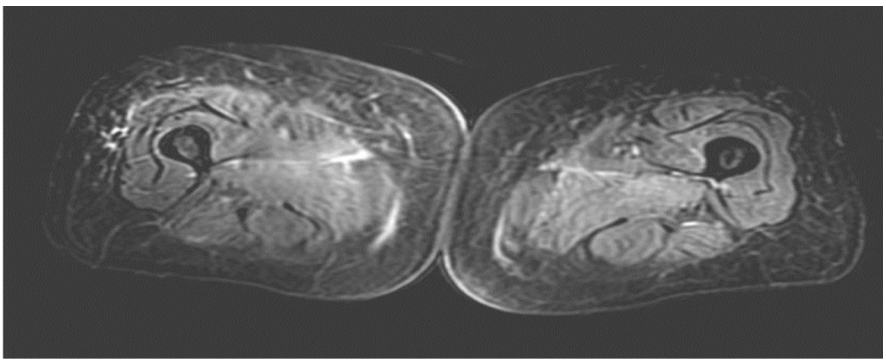

Fig. 1. Axial T2-weighted fat-suppressed MRI image of the thighs. There is bright signal in the postero-medial compartment of the musculature of thighs. This finding is not specific, but may represent an infiltrative or inflammatory process with oedema. It may be seen in polymyositis.

There are a few reports of the association of statins with inflammatory myopathies, clinical symptoms and muscle histology being much the same we observed in our case (2). Patients were severely affected, recovery was very slow after statin cessation, and corticosteroids or immunosuppressive agents were almost invariably required. The time to onset of this polymyositis-like myopathy was somewhat longer in our patient, *i.e.* two years, as compared to previously reported cases in whom it ranged from two to seven months after statin treatment was started (2). Antinuclear or other autoantibodies are common and muscle biopsies show peri-endomysial lymphocyte infiltration, atrophy and necrosis of muscle fibers (2). Search for antinuclear and other autoantibodies was, however, negative in our patient. Symptoms persist and often worsen despite discontinuing the offending statin with muscle enzymes remaining elevated for weeks or months. Complications such as an acute compartment syndrome have been reported (3). The patients recently described by Grable-Esposito *et al*. share many clinical and laboratory features with our case, however their muscle biopsies showed a severe necrotising myopathy without significant inflammation, which indicates they have a different type of statin-associated myopathy (4).

An immune-mediated mechanism is advocated in statin-associated polymyositis-like myopathy, though if statins may trigger muscle fiber apoptosis, T cell activation and MHC-I up-regulation remain unclear (5, 6). It is unknown if statins can cause by themselves or otherwise unmask an underlying immune-mediated myopathy.

Statin-associated polymyositis-like myopathy could go overlooked as patients with muscle symptoms or elevated enzyme levels do not usually undergo muscle biopsy except very severe cases. Clinicians should be aware of this disorder and muscle biopsy urgently performed in suspected cases since corticosteroids and/or immunosuppressors are required to achieve full recovery in inflammatory myopathies (7).

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