Immune Mediated Myopathy following Long-Term Statin Therapy

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Immune-mediated myopathies (IMMs) are a heterogeneous group of acute, subacute and chronic acquired diseases involving the skeletal muscle, all characterized by the presence of moderate to severe muscle weakness and inflammation. The most common IMMs are dermatomyositis (DM), polymyositis (PM), necrotizing autoimmune myositis (NAM), and inclusion body myositis. Among the IMMs, PM is rare and constitutes a single entity that often remains a diagnosis of exclusion. It occurs in subjects above the age of 18, manifesting as proximal muscle weakness, elevated creatine kinase (CK) levels, and a characteristic electromyographic pattern. Indeed, it is often misdiagnosed due to the lack of a unique clinical phenotype. In PM the fundamental immune process is mediated by CD8+ cytotoxic T cells that invade non-necrotic muscle fibers expressing major histocompatibility complex (MHC)-I antigen, whereas in dermatomyositis an abundance of B cells penetrate the fascicles between the myofibers [1].

Toxic myopathy is an uncommon side effect of statin therapy, and in most cases it presents as a self-limited condition that subsides with discontinuation of the drug. It is important to differentiate statin-associated IMMs from toxic myopathy, because patients with IMMs do not recover after discontinuing the drugs and often require immunosuppressive therapy. Among all the IMMs, polymyositis induced by statins has been described rarely in the literature [3]. We describe the case of a patient who developed biopsy-proven polymyositis following prolonged treatment with atorvastatin.

PATIENT DESCRIPTION

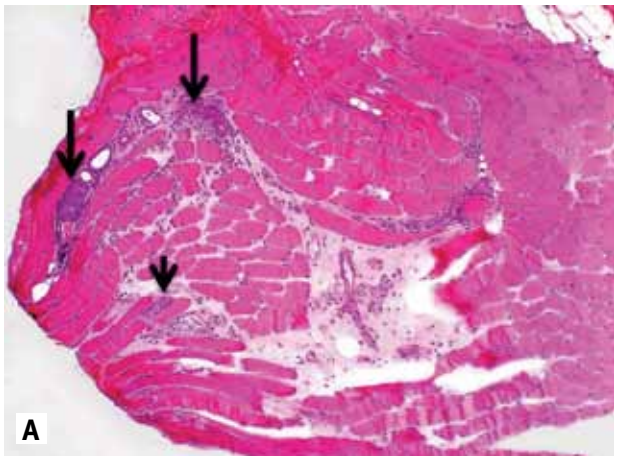
A 71 year old woman was admitted to our hospital due to weakness, myalgia, dry mouth and weight loss over the previous 3 months. Her general practitioner noticed proximal weakness, widespread tenderness and swelling of her left leg, with no other significant findings on physical examination. Initially non-steroidal anti-inflammatory drugs (NSAIDs) were prescribed but there was no significant improvement. The patient had no respiratory, abdominal or urinary symptoms, and no arthralgia, skin rash, fever, or nocturnal sweats. Her medications included atenolol 25 mg/day and atorvastatin 20 mg/day because of essential hypertension and hypercholesterolemia over the previous 5 years. There was no family history of autoimmune diseases. She was engaged in aerobic exercises three times a week, but a few weeks before admission she was unable to perform basic activities.

Blood tests revealed a significant increase in CK (> 4000 IU/L) and slightly elevated transaminases and C-reactive protein (CRP, 6.54 mg/dl). On admission, her temperature was 36.6°C, blood pressure 157/77 mmHg, pulse 70 beats/min, and weight 62 kg. On physical examination the lungs were clear, no heart murmurs were heard, lymph nodes were not palpable, and there was no hepatosplenomegaly, skin pigmentation or lesions. The only notable finding was proximal symmetric weakness of 3/5 of the four limbs with minimal swelling of the left leg.

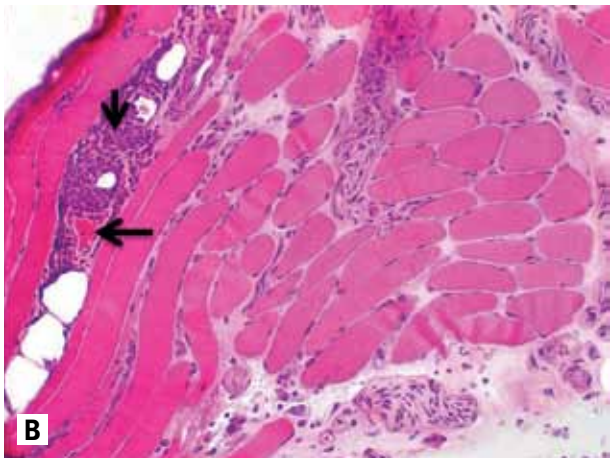
Autoantibody screening (including anti-Jo-1, anti-PL-7, anti-PL-12, anti-SRP, anti-Mi-2, anti-Ku, anti-Scl-70, anti PM-Scl) was negative except for antinuclear antibodies with a fine speckled pattern at 1:160 titer. Anti-HMG CoA reductase was also negative. The electrocardiogram was normal, a whole-body computed tomography scan did not demonstrate relevant findings and neither did a gynecological examination.

An electromyogram showed signs of myopathy with denervation features in proximal muscles of the upper limbs, while the nerve conduction study revealed superficial peroneal nerve dysfunction on the right; no further signs of neuropathy were detected. A muscle biopsy was performed, revealing several foci of endomysial perivascular infiltrate, with concomitant evidence of muscle fiber necrosis, suggestive of polymyositis [Figure 1].

Prednisone was initiated at a dosage of 60 mg/day, leading to clinical improvement and rapid decrease in levels of CK, liver function enzymes, and acute-phase reactants. Steroid tapering was subsequently performed by adding methotrexate (MTX) at the maximum dosage of 15 mg/week. After one year of surveillance the patient continues to enjoy a complete clinical remission.



[A] Low power view depicting variation in muscle fiber size along with endomysial mononuclear inflammatory cell infiltrates (long arrow) and necrotic muscle fiber (short arrow). Hematoxylin & eosin x40



[B] A higher power view demonstrates that the infiltrate is both perivascular (long arrow) and insinuating between skeletal muscle fibers within the endomysium (short arrow). Hematoxylin & eosin x100

COMMENT

Statins are commonly prescribed medications for the treatment of hyperlipidemia and have a good safety profile. However, in 5%–20% of cases the therapy has to be discontinued because of side effects [2]. One of the most common side effects involves the musculoskeletal system. Patients often complain of myalgias, but myositis and rhabdomyolysis have also been recorded. Myopathic symptoms produced by statins generally resolve within several months following cessation of the medication. Nevertheless, in rare cases statins may trigger IMMs that do not resolve despite discontinuing therapy and immunosuppressive treatment is required [2].

A recent literature review by Padala and Thomson [3] to identify statin-associated inflammatory and necrotizing myopathies yielded 10 cases of PM, 14 of DM, and 63 of statin-related NAM. Among the PM cases reported, only one was histologically well defined, six were defined as "probable" (by the presence of three of four criteria for the diagnosis of PM) and three as "possible" (by the presence of two of the four criteria), according to the Bohan and Peter diagnostic criteria [3]. In all the cases, underlying malignancy and connective tissue disorders had previously been excluded. Anti-Jo-1 was found positive only in 3 cases, while antinuclear antibodies (ANA) were positive in 6 of 10 cases. The mean duration of statin exposure symptoms was 47.8 months (range 2 weeks to 42 months) [3].

Bohan and Peter's diagnostic criteria for PM include symmetric proximal muscle weakness progressing over weeks to months; muscle biopsy showing myofiber necrosis, phagocytosis, regeneration, variation in fiber diameter, and an inflammatory exudate; elevation of serum skeletal muscle enzymes; and electromyography showing low-amplitude, small, polyphasic motor units. In our patient, all four criteria were fulfilled, confirming this as a definitive case of PM. This case report supports the fact that statin therapy could cause PM even after long-term therapy.

To the best of our knowledge, only two other similar cases have been previously described in the literature. In 2001 Folzenlogen [4] reported the case of a 76 year old man with evidence of serologically and biopsy-proven PM, responsive to both the interruption of atorvastatin and immunosuppressive treatment; Fauchais et al. [5] reported another case of probable PM in a 54 year old woman who developed proximal muscle weakness, Raynaud's phenomenon and non-specific sclerodermic changes of the hands 4 months after initiation of atorvastatin.

In conclusion, muscular symptoms in a patient on long-term statin treatment could be the first indication of polymyositis due to this treatment and should encourage physicians to perform ANA screening, especially in cases of proximal muscular weakness and increased muscle enzyme levels.

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