Immune-mediated necrotising myopathy is a rare statin-associated adverse effect: a case report

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Case report

The patient was a 60-year-old woman with a 14-year history of type 2 diabetes mellitus and dyslipidaemia with a complication of background diabetic retinopathy. In December 2016, during a routine follow-up examination, the patient was found to have asymptomatic 5-fold rise in liver aminotransferases. The patient's glycosylated haemoglobin level was 8.5% and her low-density lipoprotein cholesterol (LDL-C) level was 2.0 nmol/L. She was taking metformin 500 mg 3 times daily, gliclazide 160 mg and vildagliptin 50 mg twice daily, and atorvastatin 20 mg once daily. In view of the possibility of statin-related hepatotoxicity, atorvastatin was withheld after 22 months of treatment. However, transaminitis persisted over the following 6 months after exclusion of viral hepatitis and any structural abnormality. After 2 months, the patient complained of bilateral thigh weakness (Medical Research Council grade 4/5) and myalgia that prevented her from climbing stairs. Blood tests revealed elevated levels of creatinine kinase (CK) [5426 IU/L; normal range, 26-192 IU/L], alanine aminotransferase (294 IU/L; normal range, <47 IU/L), aspartate aminotransferase (164 IU/L; normal range, <36 IU/L), and lactate dehydrogenase (722 IU/L; normal range, 110-210 IU/L). Other inflammatory markers for myositis including anti-Jo-1 antibodies were normal. Urine for myoglobulin was negative and renal function was normal. With persistent clinical and biochemical abnormalities 9 months after statin cessation and no history of potential drug or health products that might induce myositis, immune-mediated necrotising myopathy (IMNM) associated with statins was suspected. Electromyography suggested active myopathic changes while muscle biopsy revealed atrophy of multiple muscle fibres, necrosis and regeneration without inflammatory infiltrates. Diagnosis was finally confirmed following an enzyme-linked immunosorbent assay by a marked elevation of anti–3-hydroxy-3-methylglutaryl-CoA reductase (anti-HMGCR) autoantibody to >200 IU/mL (normal range, <20 IU/mL). Considering her reasonable glycaemic control, monotherapy with intravenous immune globulin (IVIG) was initiated at a rate of 2 g per kilogram body weight per month. Muscle power increased and CK decreased (Fig) so IVIG was stopped after 6 months. Nonetheless her muscle weakness worsened and extended to involve the upper limbs as well as her ability to swallow, and CK rose from 3200 IU/L to almost 8000 IU/L after 2 months. High-dose glucocorticoids (intravenous methylprednisolone 500 mg/day for 3 days followed by oral prednisolone 45 mg/day) and cyclosporin were started. A monthly IVIG infusion was also added in the initial 2 months to enhance the therapeutic effect for her severe myopathy. After 4 months, her weakness improved and CK dropped below 1000 IU/L. Owing to deteriorating glycaemic control (glycosylated haemoglobin level deteriorated to 9.1%) and acute glaucoma, early tapering of glucocorticoid dose was considered. However, serum

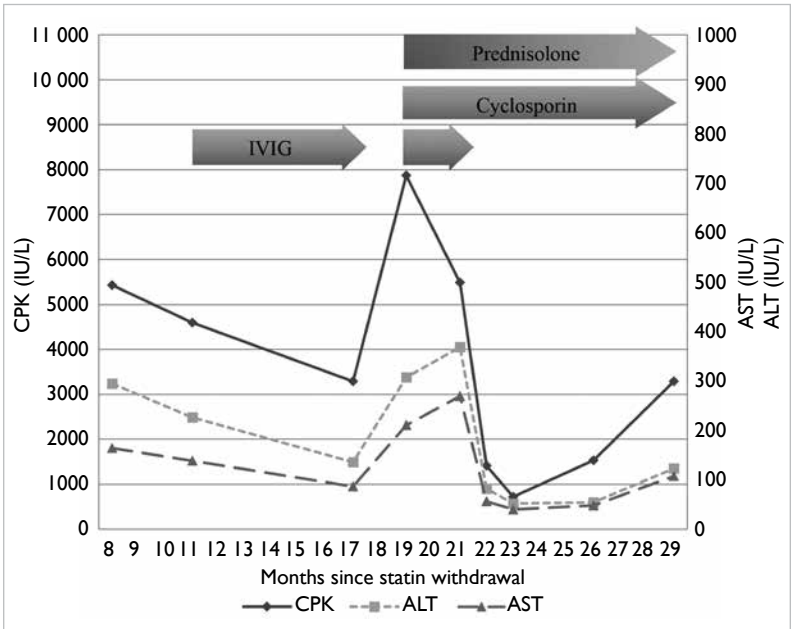

FIG. Clinical course and response to different modalities of treatment in a patient with immune mediated necrotising myopathy associated with statin use
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; IVIG = intravenous immune globulin

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CK level returned to 2000 IU/L when prednisolone dose was weaned down to 7.5 mg daily, although she retained full muscle power. Another steroid-sparing agent, either methotrexate or rituximab, was considered.

Discussion

Statins are well-proven lipid-lowering drugs that reduce LDL-C and hence cardiovascular morbidity and mortality, in both primary and secondary prevention. Their use is recommended in a wide range of patients and high intensity therapy (LDL-C reduction ≥50%) is indicated in a significant proportion.[1]

Despite their acceptable side-effect profile, about 10% of patients report statin-associated muscle symptoms (SAMS) such as myalgia and/or weakness.[2] Toxic myopathy, defined as SAMS with marked elevation (>10 times the upper limit of normal) of CK, occurs in approximately 1 in 10 000 patients treated with statins per year. Typically, this condition remits spontaneously with cessation of statin use. On the contrary, statin-associated IMNM, a rarer adverse effect with an estimated occurrence of 2 to 3 per 100 000 treated patients, is unlikely to be resolved by statin withdrawal, despite having similar SAMS and muscle enzyme increment.[3] The IMNM was only suspected in our case 9 months after cessation of statin therapy, probably due to an initial lack of SAMS and misinterpretation that the elevated aminotransferases originated from the liver rather than muscle. It is important to also check CK in asymptomatic statin users with elevated aminotransferase levels to enable early diagnosis of statin-associated myopathy.

The IMNM is now recognised as a distinct form of myositis, usually presenting with symmetrical proximal arm or leg weakness with marked elevation of CK (>10 times the upper limit of normal), muscle oedema, and atrophy on magnetic resonance imaging. In addition, muscle cell necrosis and regeneration along with minimal inflammatory infiltrates in muscle biopsy is evident and irritable myopathy on electromyography.[3] Our patient had clinical features compatible with most of these symptoms. Unlike other SAMS phenotypes, there are no identifiable risk factors such as lipophilic (vs hydrophilic) statins, high-dose statins, old age, female gender, small body frame, liver or renal failure, and concomitant medications metabolised by the same hepatic P450 isoforms[2] in statin-associated IMNM (Table). The detection of anti-HMGCR autoantibody in 2010 revolutionised the pathophysiology, diagnosis, disease classification, and treatment of this disease entity. This autoantibody detected by means of an enzyme-linked immunosorbent assay is both sensitive and specific; it has been detected in 24 of 26 patients (92%) with a clinical presentation compatible with statin-associated IMNM although it has not been detected in statin-treated patients who do not have SAMS or self-limiting toxic myopathy. The overall specificity of the commercial enzyme-linked immunosorbent assays for anti-HMGCR

TABLE. Clinicopathological characteristics of statin-associated toxic myopathy and immune-mediated necrotising myopathy

	Toxic statin myopathy	IMNM associated with statin
Estimated incidence (per year)	1 in 10 000	2-3 in 100 000
Onset	Within months after statin use	From 2 months to 10 years
Predisposing factors	• Old age • Female • Chronic renal or liver diseases • High-dose statin • Concomitant drugs metabolised by same hepatic cytochrome P450 isoforms	HLA-DRB1*11:01
Presentation	Weakness, myalgia, or both	Weakness, myalgia, or both
Creatinine kinase increment	>10 to 100 ULN	>10 to 100 ULN
Muscle biopsy	Necrotic and regenerating muscle fibres	Necrotic and regenerating muscle fibres ± sparse perivascular macrophages infiltration
Anti-HMGCR autoantibodies	Negative	Positive in >90%
Clinical and biochemical improvement after statin discontinuation	Likely	Unlikely
Treatment	Statin discontinuation	Statin discontinuation and immunosuppressants
Re-challenge with another statin	Possible	Avoid

Abbreviations: anti-HMGCR = anti–3-hydroxy-3-methylglutaryl-CoA reductase; IMNM = immune-mediated necrotising myopathy; ULN = upper limit of normal

autoantibody may be as high as 99.3%.[4] Nevertheless anti-HMGCR autoantibodies can also be detected in patients with IMNM who have an underlying malignancy or who are statin-naïve, particularly with more widespread use of anti-HMGCR autoantibody in patients with myopathy. With the detection of another autoantibody against a signal recognition particle, in 2017 the European Neuromuscular Centre classified IMNM into three subtypes: anti–signal recognition particle myopathy, anti-HMGCR myopathy and antibody-negative IMNM.[3] Although these subtypes share similar clinical features to those mentioned above, they differ in environmental risk factors, genetic risk factors, cancer risks, extra-muscular manifestations, and response to different treatment modalities and prognoses.

Although spontaneous improvement after statin cessation has been reported in case studies, most patients with this condition require one to two immunosuppressive agents, usually in the form of high-dose glucocorticoids plus one of the following; methotrexate, azathioprine, mycophenolate mofetil or cyclosporine, for initial disease control.[4,5] The IVIG has also been used successfully as first-line monotherapy and it may be considered in those with pre-existing diabetes, as in our patient.[6] However, incomplete normalisation of CK and the need for a prolonged course of treatment suggests its inability to completely abolish the pathophysiological process that causes muscle damage. This was illustrated in our patient with a rebound in CK level 2 months after completion of a 6-month course of IVIG monotherapy. Rather, her condition stabilised following treatment with two immunosuppressants, prednisolone and cyclosporine, although her anti-glycaemic treatment needed to be intensified. Similar to the clinical course of other reported series, her condition relapsed upon weaning of glucocorticoid dosage.[7] Apart from escalation of steroid dosage, other steroid sparing agents may need to be considered. Rituximab has emerged as a promising rescue agent in this situation.[8] Lastly, as statin is a known trigger of anti-HMGCR autoantibody, re-challenge with any statin should be avoided and an alternative cholesterol-lowering agent such as ezetimibe or PCSK9 inhibitors can be considered.[9]

In conclusion, IMNM can occur rarely in patients who present with SAMS. Unlike toxic myopathy, clinical and biochemical abnormalities persist upon statin withdrawal and immunosuppressants are usually required for disease control.

Author contributions

All authors contributed to the concept or design of the study, acquisition of the data, analysis or interpretation of the data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

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Ethics approval

The patient was treated in accordance with the Declaration of Helsinki. The patient provided written informed consent for all treatments and procedures.

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