

# Statin-induced myopathy: a case report

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## Background

Statins are one of the most frequently used drug groups among patients with cardiovascular disease. Muscle pain is very frequent among patients using statins. It is important to distinguish patients with benign muscle pain without significant biochemical correlates from patients with serious myopathies.

## Case summary

We present the case of a 68-year-old woman taking atorvastatin in the past 8 months after a coronary bypass grafting, presenting with proximal muscle weakness and pain. Biochemical analysis showed a markedly elevated creatine kinase (CK) (24,159 U/L). Despite discontinuation of the statin and therapy for rhabdomyolysis (IV fluid, mannitol, and sodium bicarbonate), CK levels did not drop as much as expected. Muscle biopsy showed mild inflammatory changes and few necrotic muscle fibres, suggestive for an immune-mediated necrotizing myopathy (IMNM). Serology showed a high anti-HMG-CoA reductase antibody (anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase antibody) titre, diagnostic for an IMNM induced by statins. The patient was treated with corticosteroids and methotrexate. Creatine kinase levels, muscle weakness, and pain gradually improved over the following months.

## Discussion

IMNM induced by statins is a relatively new entity. It is important to be recognized because it is not a self-limiting adverse effect such as the frequent benign muscle pains caused by statins. Beside discontinuation of the causative statin, aggressive immunosuppressive therapy is mandatory in IMNM. Therefore, it is important to test for anti-HMGCR antibodies and if necessary perform a muscle biopsy in patients taking statins, presenting with muscle weakness, and CK elevations not improving after discontinuation of the statin.

## Keywords

Statin • Myopathy • Immune-mediated necrotizing myopathy • Anti-HMGCR antibodies • Case report

## Learning points

- It is important to recognize an immune-mediated necrotizing myopathy (IMNM) associated with anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (anti-HMGCR) antibodies in patients taking statins with muscle weakness and creatine kinase elevation not resolving after discontinuation of statins.
- Here, it is required to test for anti-HMGCR antibodies and if necessary perform a muscle biopsy.
- In patients with an IMNM associated with anti-HMGCR antibodies, there is a need for aggressive immunosuppressive therapy, beside discontinuation of the causative statin.

## Introduction

Statins have proved to significantly reduce cardiovascular risk in primary and secondary prevention.<sup>1</sup> However, muscle pain is a frequent adverse effect of statins with an incidence of about 15%.<sup>2</sup> It is important to differentiate benign muscle pain without biochemical abnormalities from severe myopathies in which discontinuation of statin use is mandatory and in which active therapy could be mandated.

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## Timeline

Eight months prior to presentation	Unstable angina pectoris. Coronary angiography shows a critical left main coronary artery stenosis Semi-urgent coronary artery bypass graft Hypercholesterolaemia was detected and atorvastatin (80 mg once a day) was started.
Upon presentation to emergency room	Proximal muscle weakness and pain in both legs in the past week with the inability to perform daily life activities. She was not able to walk more than 20 m. Patient was admitted at the intensive care unit and treated with IV crystalloids, mannitol, and sodium bicarbonate. Atorvastatin was stopped.
Day 4	Muscle biopsy was performed. Electromyography: suggestive for an irritable myopathy Corticosteroids were started (methylprednisolone 64 mg orally) Discharge from the intensive care unit
Day 8	Muscle biopsy: mild infiltration with white blood cells and few necrotic muscle fibres
Dag 14	Significantly elevated anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase antibody titre
Day 17	Liver biopsy showed no abnormalities
Day 18	Discharge from hospital
Three months after presentation	Methotrexate was started
One year after presentation	The patient can easily walk up to 250 m.

## Case summary

We present the case of a 68-year-old woman with a history of arterial hypertension, hypercholesterolaemia, and coronary artery bypass grafting. Her medication was perindopril 2.5 mg once a day (o.d.), bisoprolol 2.5 mg o.d., atorvastatin 80 mg o.d., pantoprazole 40 mg o.d., acetylsalicylic acid 80 mg o.d., flurazepam 27 mg o.d., and bromazepam 6 mg o.d.

She presented with progressive symmetric proximal muscle weakness and pain in both legs and to a lesser extent in both arms in the week prior to presentation. She was not able to walk more than 20 m. There was no prior trauma or strenuous exercise. There were no other neurological symptoms, fever, dysphagia, chest pain, palpitations, or shortness of breath. There was no history of malignancy, auto-immune disease, and no family history of neuromuscular disorders.

Physical examination demonstrated reduced muscle power symmetrically in both upper legs (scored 4 out of 5) without any weakening in the upper limbs (strength scored 5 out of 5). There were no fasciculations, swelling of the affected muscles, or skin rash. Reflexes were universally weak. There were no sensory or visual deficits. Heart and lung auscultation and abdominal examination revealed no abnormalities. Her heart rate (80 b.p.m.), blood pressure (134/75 mmHg), oxygen saturation (95 %), and respiratory rate (14 breaths per minute) were unremarkable.

Laboratory workup showed an elevated creatine kinase (CK) (24, 159 U/L, reference value <170 U/L), aspartate transaminase (1211 U/L, ref. <32 U/L), and alanine transaminase (475 U/L, ref. <31 U/L), C-reactive protein (116 mg/L, ref. <5 mg/L), and high sensitive Troponin T (274 ng/L, ref. <14 ng/L). Gamma-glutamyl transferase was slightly increased and bilirubin was normal. Abdominal ultrasound and chest X-ray showed no abnormalities. Electromyography showed abnormal spontaneous muscle activity in all examined muscles (fibrillations, positive sharp waves, and pseudomyotonic discharges), suggestive for an irritable myopathy.

Electrocardiography showed an incomplete right bundle branch block with inverted T waves in leads V1–V5, which were known and were unchanged for this patient. Troponin T levels were moderately elevated during the admission (with a maximum of 383 ng/L). Echocardiography showed no global or regional contractility disorders and no structural abnormalities. End-diastolic left ventricular diameter was 44 mm and posterior wall thickness was 11 mm. In the absence of echocardiographic disorders, chest pain and electrocardiographic changes, we supposed the elevated troponin values could be explained by a clinically insignificant myocarditis.

The patient was admitted for 4 days to the intensive care unit to monitor diuresis, fluid balances, arterial and urinary pH, electrolytes, and kidney function. Therapy was given for rhabdomyolysis: large amounts of IV crystalloids (2 L per day), mannitol (15% 100 mL four times a day), and sodium bicarbonate (50 meq NaHCO<sub>3</sub> over 15 min followed by 10 meq/h with regular control of urinary pH, arterial pH, and arterial sodium). Atorvastatin was discontinued. Muscle pain improved and CK-level rapidly halved in the first 3 days of admission but unexpectedly stabilized (at 13 008 U/L) during the following days despite therapy (Figure 1). At that moment, an inflammatory myopathy was suspected and a muscle biopsy was performed. Furthermore, corticosteroids were started.

A workup was performed in search of the cause of the inflammatory myopathy. X-ray of all four proximal extremities showed no evidence of calcifications typical for dermatomyositis. Serologic examination (Epstein–Barr, herpes simplex, cytomegalo- and adenovirus, hepatitis B and C virus, HIV, mycoplasma, Coxsackie, (para)-influenza, and Echinococcus) showed no significant abnormalities. CA 125 and CA 19.9 were normal and there were no obvious signs of malignancies. Anti-nuclear antibodies were weakly positive (1/80). All myositis-specific auto-immune serology was negative (anti-Mi2, MDA5, NXP2, TIF1, SAE, anti-striated muscle antibodies, antisynthetase antibodies, and anti-Signal Recognition Particle (anti-SRP)), except for anti-HMGCR antibodies (anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase antibodies), which were highly elevated.

Muscle biopsy showed mild infiltration with white blood cells and few necrotic muscle fibres (Figure 2), suggestive for an

immune-mediated necrotizing myopathy (IMNM). Due to the clinical and biochemical presentation, the typical muscle biopsy findings and the elevated anti-HMGCR antibodies, the diagnosis of HMGCR antibody-mediated IMNM was presumed.

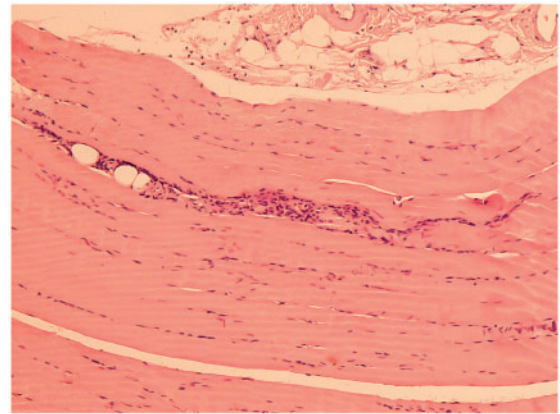
Methylprednisolone 64 mg o.d. orally was started 3 days after admission. Muscle pain disappeared during admission. Methylprednisolone was reduced to 48 mg after 1 month and further slowly tapered. One year after initial presentation, she received methylprednisolone 4 mg weekly. Creatine kinase levels further dropped and normalized 3 months after presentation. After 3 months methotrexate (2 × 7.5 mg once a week) was started to taper the steroid dose and because of the ongoing muscle weakness.

The patient received intensive physiotherapy. Muscle weakness slowly improved during the following year. After 1 year, she could walk short distances (up to 250 m). Muscle strength scored 4 to 5 out of 5 in the lower limbs and 5 out of 5 in the upper limbs.

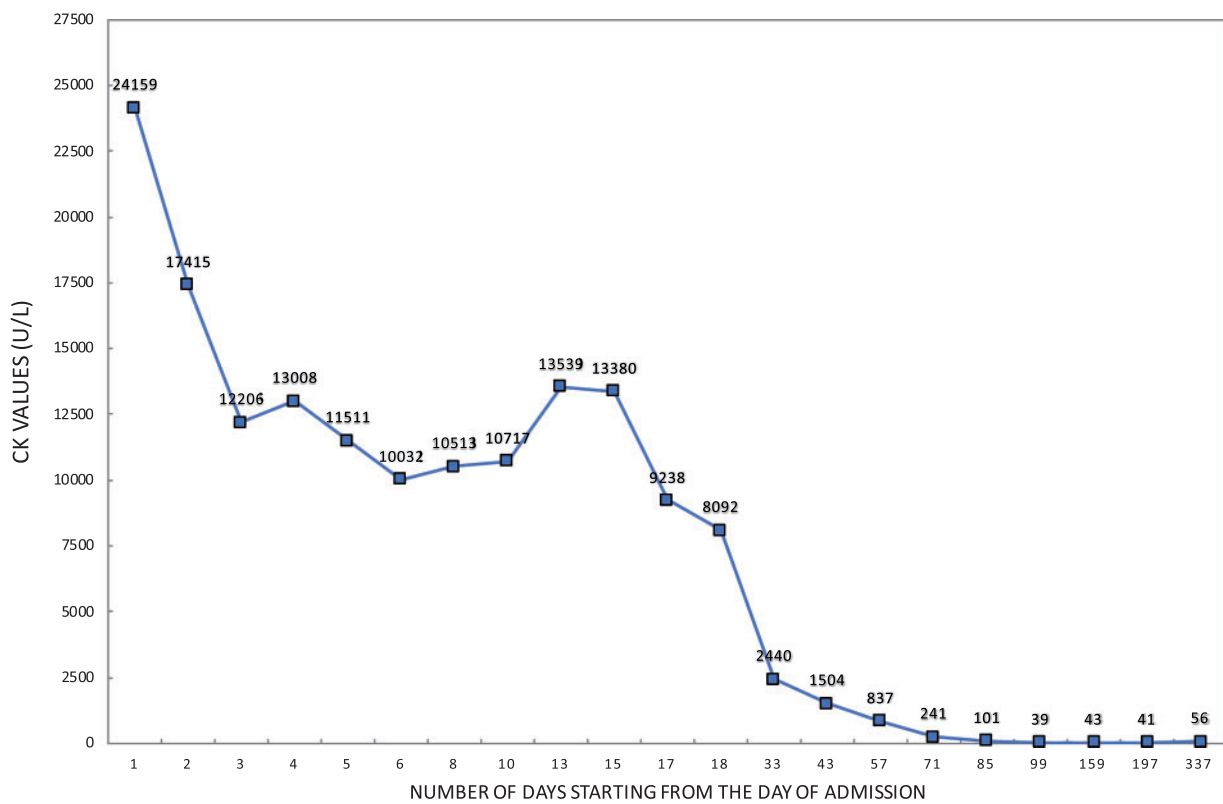
## Discussion

The differential diagnosis of idiopathic inflammatory myopathies comprises polymyositis, dermatomyositis, IMNM, inclusion body myositis, non-specific myositis, and antisynthetase syndrome.<sup>3-5</sup> Immune-mediated necrotizing myopathy can be associated with anti-HMGCR antibodies, anti-SRP auto-antibodies, HIV and hepatitis C virus (HCV) infection, other connective tissue disorders (i.e. scleroderma), paraneoplastic disease, or it may be idiopathic.<sup>5,6</sup> Muscle biopsy

typically shows necrotic muscle fibres, muscle cell regeneration, and only a mild or absent infiltration of inflammatory cells.<sup>5,7,8</sup> In patients with IMNM and anti-HMGCR antibodies, statin use is present in 37.5–94% according to several studies, much more than in other inflammatory myopathies.<sup>4,7</sup> Patients without prior statin use are younger and are less responsive to treatment.<sup>5,7</sup>



**Figure 2** Muscle biopsy with haematoxylin and eosin staining showing mild infiltration with white blood cells and few necrotic muscle fibres.



**Figure 1** Creatine kinase levels starting from the day of admission.

Immune-mediated necrotizing myopathy associated with statin use and anti-HMGCR antibodies was first described in 2010 by Christopher-Stine *et al.*<sup>9</sup> It is characterized by an acute (days to weeks) or subacute (<6 months) onset of mild to moderate symmetrical muscle weakness.<sup>4,5,8</sup> Despite the usually mild muscle weakness, high CK values are present, frequently more than 10 times the upper limit of the normal range.<sup>4,5,8</sup> The incidence is only 2–3 of every 100 000 patients treated with statins and it is more frequent above the age of 50 years.<sup>8–10</sup> Organ involvement (skin, lung, or heart) is not typical for HMGCRAntibody-mediated IMNM.<sup>3</sup> The duration of exposure to statins before presentation varies from 2 months to 10 years, with an average of 3 years.<sup>11</sup> Anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase antibodies cannot be found in statin-exposed subjects without myopathy and in patients with a self-limited statin myopathy.<sup>12</sup>

Typical of HMGCRAntibody-mediated IMNM is the ongoing muscle weakness and elevated CK despite discontinuation of the statin.<sup>11</sup> This could be explained by an up-regulated expression of HMGCRAntibody-mediated IMNM on muscle cells induced by statin use, which is the pharmacologic target of statins and presumably the trigger for the autoimmune response.<sup>10</sup> Furthermore, regenerating muscle cells have a higher expression of HMGCRAntibody-mediated IMNM despite discontinuation of statins, which causes a further ongoing trigger for the immune system. This is in contrast with the more frequent self-limiting myopathies caused by statin use, which resolve after several weeks or months after statin discontinuation.

There are no randomized controlled trials concerning the therapy of HMGCRAntibody-mediated IMNM. Usually corticosteroids are being prescribed, often with a modest initial response.<sup>4,8</sup> Addition of other immunosuppressive drugs is frequently necessary to control the disease. Treatment with methotrexate, intravenous immunoglobulins, azathioprine, cyclosporin, mycophenolate mofetil, plasmapheresis, and rituximab were reported.<sup>4,5,8</sup> Relapse of IMNM after tapering of the therapy or re-exposure to statins is frequent but it is unknown whether patients can safely be rechallenged with statins or other cholesterol-lowering agents.

Statin-mediated myopathies are diverse and can be divided into benign muscle pain without CK elevation, myopathy/myositis with significant CK elevation, fulminant rhabdomyolysis, and HMGCRAntibody-mediated IMNM.<sup>7</sup> The 2016 ESC clinical practice guidelines on the management of dyslipidaemias<sup>1</sup> comprise a strategy for managing patients taking statins with high CK levels.

## Conclusion

In conclusion, it is important for cardiologists to recognize a HMGCRAntibody-mediated IMNM in patients with muscle weakness and CK elevation not resolving after discontinuation of statins, the more if CK elevation does not improve after 8 weeks.<sup>8</sup> In these cases, anti-HMGCRAntibodies should be tested and if necessary a muscle biopsy should be performed.

## Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

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**Slide sets:** A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

**Consent:** The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

**Conflict of interest:** none declared.

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