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Case Report

# Statin-induced Myonecrosis—A Rare Adverse Effect of a Common Drug: A Case Report

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## Abstract

**Background:** Clinically significant statin-induced myonecrosis is a rare clinical disorder that affects the skeletal muscles of patients taking statin medication. Its clinical presentation ranges from mild muscle pain to muscle weakness associated with significant elevation (>10×) of serum creatinine kinase (CK). Early screening, identification, and treatment of statin-induced myopathy are vital as it may lead to drug discontinuation and poor medication adherence.

**Case Report:** We report a 40-year-old male diabetic patient who visited our neurology referral clinic with a two-week history of muscle pain associated with proximal extremities' weakness, which later progressed to involve the distal extremity muscles of his upper and lower limbs. A week before his presentation to our hospital, he became wheelchair-bound. Six months before his admission, he was started on a daily dose of 40 mg oral simvastatin for prevention, given his cardiovascular risk factors. No history of fever, headaches, abnormal body movement; no personal or family history of similar illness; no history of trauma, alcohol use, smoking, or use of herbal medication was elicited. His CK levels were elevated 19 times, and electromyography examination showed a myopathic pattern in proximal muscles. Following the discontinuation of simvastatin, the patient's muscle weakness significantly improved. In addition, his serum CK levels also lowered significantly on his follow-up evaluation.

**Conclusion:** This case describes a diabetic patient with statin-induced myonecrosis, managed conservatively through statin withdrawal. It also highlights the benign prognosis in younger patients, showing that the condition generally has a favorable outcome with timely diagnosis and management.

**Keywords:** statin, myonecrosis, myopathy, diabetes mellitus, creatinine phosphokinase

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## 1. Introduction

Statin is the most common primary and secondary prevention therapy for cardio-metabolic disorders and is often deemed safe for most patients [1]. Rarely, statin may induce inflammation of skeletal muscles (myositis), which primarily manifests as myalgia, muscle tenderness, weakness, and substantially elevated (10× increased) creatinine kinase (CK) concentration. CK is found mainly in muscle fibers and significantly increases following muscle damage [1–4]. Clinically significant statin-induced myonecrosis is a rare clinical disorder that affects the skeletal muscles of patients taking statin medication. Its clinical presentation ranges from mild muscle pain to muscle weakness associated with significant elevation of serum CK [5, 6]. Data from observational studies indicate that the prevalence of this disorder is between 10% and 15%, while clinically significant myonecrosis, defined as a serum CK elevation >10× the normal amount in association with muscle symptoms, occurred in <0.5% of patients. [7–11].

Risk factors for statin-induced myopathy may include advanced age, female gender, a history of major surgeries, and hypothyroidism [1–4, 10–12]. Stain-related risk factors are also identified: Hydrophilic statin drugs such as pravastatin, fluvastatin, and rosuvastatin are less commonly associated with myonecrosis than lipophilic statin drugs like atorvastatin, simvastatin, and lovastatin [1–4, 10–12].

The pathophysiology and mechanism by which statins cause muscle toxicity is a point of continuing investigation. Central to most of the proposed mechanisms is the distinct effect of individual statins on the synthesis of coenzyme Q10 (CoQ10 or ubiquinone), which plays an important role in muscle cell energy production. It is speculated that a reduction in ubiquinone may contribute to statin-induced muscle injury. Studies have come to different conclusions about whether statin treatment decreases ubiquinone levels in skeletal muscles [7–10]. Long-term treatment with simvastatin (10–40 mg daily for over 12 months) reduced ubiquinone content and decreased maximal mitochondrial oxidative phosphorylation capacity [7–10].

Variations in presentation may be related to variations in the genetics of statin clearance, metabolism, transport, and/or action (i.e., cytochrome P450 genes including *CYP3A4*, *CYP3A5*, *CYP2D6*, and the vitamin D-receptor gene). This points to the fact that statin myopathy may be precipitated by the concomitant use of cytochrome-450 inhibitors (particularly CYP3A4, which metabolizes the lipophilic statins) like protease inhibitors, macrolides, and nondihydropyridine calcium channel blockers (CCBs). Additive myocyte toxicity has also been reported with the concomitant use of corticosteroids, fibrates, and colchicine.

Hence, early screening, identification, and treatment of statin-induced myopathy are vital, as it may lead to drug discontinuation and poor medication adherence.

## 2. Case Report

### 2.1. Patient presentation

A 40-year-old, right-handed, diabetic male patient who had received subcutaneous insulin therapy in the form of NPH 50/36 and metformin 500 mg daily for 19 years, presented with a two-week history of muscle pain associated with proximal extremities weakness, which later progressed to involve the distal extremities' muscles of the upper

and lower limbs. A week before his presentation to our hospital, he became wheelchair-bound. Six months before his presentation, considering his high cardiovascular risk score, he had been started on oral simvastatin 40 mg daily for the primary prevention of atherosclerosis. In addition, he reported reddish discoloration of urine and had also been recently treated for pneumonia with an unspecified antibiotic regimen. No history of fever, headaches, abnormal body movement, trauma, alcohol use, smoking, use of herbal medication, or personal or family history of similar illness was reported.

## 2.2. Clinical examination

The patient's blood pressure was measured at 140/90 mmHg, pulse rate at 80 bpm, respiratory rate at 20 breaths per minute, and temperature at 36.7°C. Examination revealed grade 1 non-pitting pedal edema, muscle tenderness, and hyperalgesia. Motor examination showed normal tone and reduced reflexes. Power was 3/5 and 4/5 in proximal and distal upper limbs, respectively, and 2/5 and 3/5 in proximal and distal lower limbs, respectively.

## 2.3. Diagnostic investigations

Laboratory investigation showed 19 times elevated CK levels and 15 times elevated alanine aminotransferase (ALT). The detailed list of investigations has been summarized in Table **1**. Electromyography (EMG) examination showed a myopathic pattern in the proximal muscles (e.g., deltoid; Figure **1**). Considering the clinical, laboratory, and electrophysiological evidence, a diagnosis of probable statin-induced myonecrosis was made. Given the patient's longstanding history of diabetes mellitus, diabetic myonecrosis (DM; diabetic muscle infarction) was strongly considered as a possible differential diagnosis.

## 2.4. Management

Simvastatin was discontinued, and the patient was started on symptomatic treatment and advised to continue insulin and oral glycemic drugs. Following this, he showed significant clinical and biochemical improvement. On follow-up evaluation after four weeks of statin discontinuation, muscle power was normal in all his extremities, and his CK and liver enzymes were reduced (Table **1**).

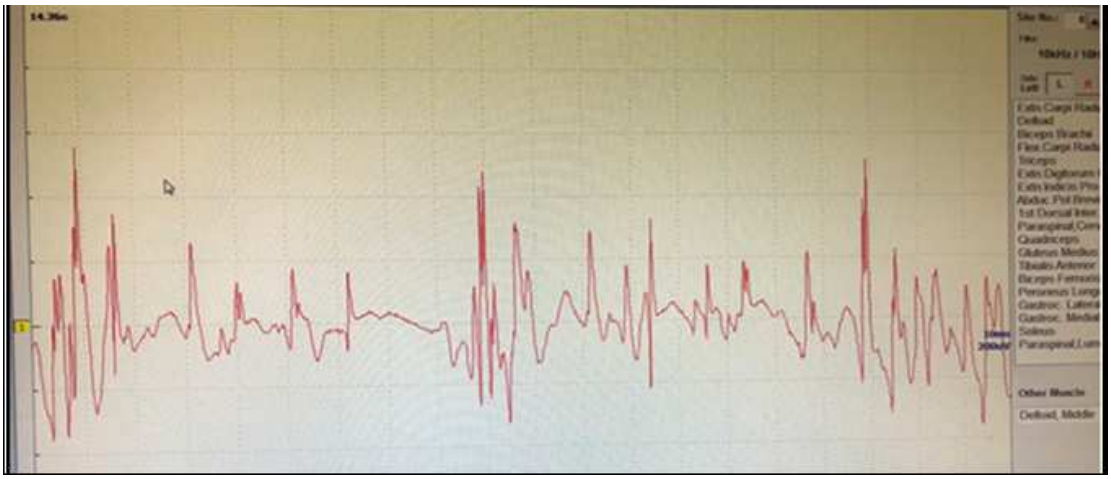

**Figure 1**: Electromyography examination showing small amplitude and short duration muscle unit action potential (MUAP) with early recruitment and many polyphic potentials from the left deltoid muscle.

**Table 1**: Laboratory results of the patient and reference values.

| Laboratory tests | At presentation | At follow-up evaluation (2 weeks) | Normal reference values (ABIM* 2024) |
|---|---|---|---|
| White blood cells count (cells/mL) | 13,100 | 7100 | 5000–11,000 |
| Hemoglobin (g/dL) | 14.5 | 14.2 | 14–16 |
| MCV (fL) | 91.27 | 98 | 80–99 |
| Platelets count (cells/mL) | 466,000 | 234,000 | 150,000–350,000 |
| CK | 4204 (19× ↑ UNL) | 514 ( 2.3× ↑ UNL) | 55–170 |
| AST | 210 (5× ↑ UNL) | 40 | 10–40 |
| ALT | 595 (15× ↑UNL) | 66 (1.5× ↑UNL) | 10–59 |
| Alkaline phosphatase (U/L) | 165(1.8× ↑UNL) | 83 | 20–140 |
| Total bilirubin (mg/dL) | 0.3 | 0.4 | 0.2–1.3 |
| Direct bilirubin (mg/dL) | 0.08 | 0.08 | 0.0–0.3 |
| Albumin (g/dL) | 2.8 | 2.8 | 3.5–5.0 |
| Sodium (mmol/L) | 131 | 137.2 | 135–146 |
| Potassium (mmol/L) | 4.41 | 4.35 | 3.5–4.5 |
| Chlorine (mmol/L) | 98 | 101.6 | 96–106 |
| Urine analysis | | | |
| Protein | Negative | Negative | Negative |
| Glucose | Negative | 3+ | Negative |
| Ketone | Negative | Negative | Negative |
| Leukocyte | Negative | Negative | Negative |
| Nitrite | Negative | Negative | Negative |
| Blood | 2+ | Negative | Negative |
| Erythrocyte sedimentation rate (mm/hr) | 60 | | 0–20 |
| Blood urea nitrogen (mg/dL) | 14 | | 5–18 |
| Creatinine (mg/dL) | 0.4 | | 0.5–1.2 |
| HBSAg | Negative | | |
| Hepatitis C virus antibody | Negative | | |
| HIV serology | Negative | | |

*ABIM: American Board of Internal Medicine
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatinine kinase; HBSAg, hepatitis B surface antigen; MCV, mean corpuscular value

## 3. Discussion

Clinically-significant statin-induced myonecrosis is a rare clinical disorder that affects skeletal muscles of patients taking statin medication. Its clinical presentation ranges from mild muscle pain to muscle weakness associated with significant elevation (>10×) of serum [5, 6]. The present case describes a 40-year-old diabetic patient who was on statin therapy (simvastatin) for six months and presented with clinical features of myonecrosis: progressive muscle pain, proximal muscle weakness, and 19 times elevated serum CK. Likewise, the EMG examination from the proximal muscles showed

a myopathic pattern. Furthermore, the patient's clinical symptoms significantly improved following the discontinuation of the statin drug. In addition, the serum CK levels returned to normal on subsequent follow-ups. Advanced age is one of the well-known risk factors for statin-induced myonecrosis [4–6, 9–12]. However, the present case describes a relatively young patient in his forties and suggests a possible demographic heterogeneity in statin-induced muscle diseases.

Statin-induced muscle disease has a heterogeneous clinical and biochemical presentation, ranging from myalgia (muscle pain) to myonecrosis associated with rhabdomyolysis [5, 6, 10]. Furthermore, the biochemical profile of statin-induced myopathy may range from no elevation of CK to >20 times the elevation of CK. The present case has fulfilled the clinical and biochemical criteria of statin-induced myonecrosis without evidence of rhabdomyolysis and acute kidney injury. However, the patient has a history of reddish urine discoloration, which could indicate some degree of rhabdomyolysis not severe enough to induce acute renal failure. In this case, the EMG findings from the proximal muscles show electrophysiological evidence of myopathy, such as motor unit action potential (MUAP) of short duration, low amplitude, polyphasic, and early recruitment (Figure **1**). This is congruent with previous reports, which support the presence of myopathic EMG patterns in patients with a severe form of statin-induced myopathy, such as myonecrosis [3, 5, 6, 9, 12, 13]. Nevertheless, in most cases, statin□induced myopathy is primarily associated with damage to the type II muscle fibers, hence normal EMG findings. However, in severe forms such as statin-induced myonecrosis, electrophysiological evidence of myopathy is not uncommon [3, 5, 6, 9, 12, 13].

In the present case, considering the presence of long-standing comorbid diabetes mellitus, it is vital to consider DM as one of the most critical potential differential diagnoses [14]. DM occurs primarily due to diabetic vasculopathy, causing the infarction of skeletal muscles, predominantly in proximal lower-limb muscle groups [14]. Furthermore, DM classically manifests as muscle pain, tenderness, and swelling. This is while the present case was mainly presented with mild myalgia and proximal muscle weakness without muscle swelling. Furthermore, this patient had a history of good glycemic control and no muscle swelling, and both his upper and lower limb muscles were affected, making DM a diagnosis that is less likely than statin-induced myopathy. Apart from diabetic muscle necrosis, other differential diagnoses include various causes of muscle necrosis, such as trauma, infection, ischemia, and malignant necrosis. However, our case presents with none of these risk factors, historically or on physical examination.

Several management options have been suggested for managing dyslipidemia in patients who recovered from statin-induced myopathy, including rechallenging with a low dose of statin every other day, ezetimibe, and starting a non-statin-based therapy [2, 5, 6, 11, 12, 14–16]. In the present case, the planned management for dyslipidemia is to start the patient on another class of statin with a low risk of myopathy once the patient has fully recovered from the present illness. To prevent complications associated with statins, it is advisable to obtain a thorough medical history before starting statin therapy and assess risk factors that may contribute to statin-induced myonecrosis, like drug–drug interactions, thyroid dysfunction, or renal impairment. If myonecrosis has occurred previously, these factors should be evaluated before considering rechallenge with

statins. In severe cases, clinicians need to consider alternatives to statins, such as PCSK9 inhibitors, for dyslipidemia control [17].

## 4. Conclusion

This case describes a diabetic patient with statin-induced myonecrosis, managed conservatively and statin withdrawal, and highlights the benign prognosis in younger patients. Overall, statin-induced myonecrosis has a favorable prognosis given timely diagnosis, intervention, and management.

## Declarations

## Acknowledgments

The authors would like to thank the patient for his cooperation.

## Ethical Considerations

The authors' institution does not require ethical approval to publish a single case report. Written informed consent was obtained from the patient's family to publish this case report and any accompanying images. A copy of the written consent is available from the corresponding author upon reasonable request.

## Competing Interests

The authors declare no competing interests.

## Availability of Data and Materials

All data sets on which the conclusions of the case report are based are available as a medical record document from the corresponding author on reasonable request from the editors.

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None.

## Abbreviations and Symbols

ABIM: American Board of Internal Medicine

ALT: Alanine aminotransferase

AST: Aspartate aminotransferase

CCB: Calcium channel blocker

CK: Creatinine kinase

DM: Diabetic myonecrosis

EMG: Electromyography

HBSAg: Hepatitis B surface antigen

MCV: Mean corpuscular value

MUAP: Muscle unit action potential

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