Aggressive and fatal statin-induced dermatomyositis: a case report

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Abstract
Statins are widely used and are currently the state-of-the-art treatment for primary and secondary prevention of cardiovascular disease. Although statins are generally well tolerated and present an excellent safety profile, adverse effects from muscle toxicity may occur in some patients. Statin-induced dermatomyositis (DM) is a rare adverse event associated with its use and very few fatal cases have been reported. We present the case of a 69-year-old man with early onset DM precipitated by a small dose of simvastatin. Despite immediate cessation of the agent and the use of systemic corticosteroids, the case took a very aggressive and fatal course. Such progression is extremely unusual for statin-induced DM. Despite the safety of statins, we highlight the importance of identifying potential side effects associated with this class of medications. We also emphasize the importance of correct diagnosis and close follow-up of patients with statin side effects.

INTRODUCTION
Statins are currently the state-of-the-art in pharmaceutical intervention for reducing the probability of cardiovascular disease (CVD) events in patients with moderate or high risk. Substantial evidence indicates the safety of statins, with myalgia as the most commonly reported side effect. Severe muscular side effects are rare and fatal events are unusual. We present the case of a 69-year-old man with early onset dermatomyositis (DM) precipitated by a small dose of simvastatin. Despite immediate cessation of the agent and early institution of immunosuppressive therapy, the outcome was unfavorable.

CASE REPORT
A 69-year-old man presented with a 1-week history of erythroderma, which began 3 days after the prescription of simvastatin (20 mg/day) for primary prevention of CVD (Fig. 1). His comorbidities included hypertension, Type 2 diabetes-mellitus, and chronic obstructive pulmonary disease due to a history of smoking. Statin therapy was immediately discontinued and he was treated with systemic corticosteroids (prednisone 1 mg/kg/day) with initial improvement.

After a 2-month period on a progressively reduced steroid dosage, the patient was admitted to the hospital due to muscle weakness and ulcer formation at the site of his previous rash. Physical examination also revealed heliotrope rash, Gottron’s papules and periungual telangiectasias (Fig. 2). Muscle testing found evidence of proximal muscle weakness affecting the hip and shoulder girdles. There was no fever, calcinosis, Raynaud’s phenomenon, dyspnea or sclerodactyly.

Laboratory evaluation showed elevated levels of creatine kinase (CK) (617 mg/dl) and CK-MB enzymes (50 mg/dl). The
anti-histidyl-tRNA synthetase (anti-Jo-1) and anti-Mi-2 auto-antibodies were negative. There was no evidence of cardiologic, rheumatologic or infectious disease. Malignancy work-up was performed with contrast-enhanced chest and abdomen computed tomography. He also underwent upper and lower gastrointestinal endoscopy showing no signs of malignancy. Additionally, levels of available tumor markers (CA19-9, carcinoembryonic antigen, lactate dehydrogenase, prostate-specific antigen, thyroglobulin) were all non-suggestive of neoplasm. An ulcer biopsy revealed basal layer vasculopathic degeneration of keratinocytes with eosinophilic infiltrate and leukocytoclastic vasculitis. A deltoid muscle biopsy was performed, showing nonspecific findings. However, a muscle MRI revealed areas of fatty infiltration and muscle edema (Fig. 3).

Statin-induced DM was diagnosed. Despite high-dose methylprednisolone therapy, only mild clinical improvement was observed over the next two weeks. The patient developed dysphagia and rapidly progressed to aspiration pneumonia and sepsis. Additional treatment with high-dose corticosteroids or other immunosuppressive drugs was not possible. The patient died several days later.

DISCUSSION

Statins, or 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are currently the preferred pharmaceutical intervention for reducing the probability of CVD events and mortality by at least a moderate amount in adults aged 40–75 years who have one or more CVD risk factors and a calculated 10-year CVD event risk of at least 10%.

Substantial evidence indicates the safety of statins, with myalgia as the most commonly reported side effect [1]. However, statin-associated auto-immune myopathy has also been observed. The recommended classification is to break down this spectrum of diseases into inflammatory myopathies (polymyositis and DM) and necrotizing myopathy [2–4]. Although its incidence is not known with certainty, data suggest that it occurs in ~2–3 of every 100,000 patients treated with statins. Fatal cases are extremely rare, occurring in only 0.2 or fewer instances per million statin prescriptions [5–7].

The present report highlights a rare case of fatal DM precipitated by small dose of simvastatin. Statin-induced DM is believed to be an auto-immune skeletal muscle disorder. It usually manifests from 2 months up to 5 years after initiation of statin therapy, although there are case reports showing earlier symptom onset [8]. Typical features of DM include muscle pain, weakness and tenderness, which are proximal and symmetrical. Unique dermatological features usually accompany muscle weakness and are pathognomonic of the disease. These include scaly erythematous lesions found on the extensor surfaces of the metacarpophalangeal, proximal interphalangeal and distal interphalangeal joints known as Gottron’s papules. Moreover, patients may develop a violaceous eruption on the upper eyelids, sometimes associated with periorbital edema, known as heliotrope rash [9].

In typical cases of DM, elevated levels of CK and other muscle enzymes are common. As expected in auto-immune diseases, patients have unique auto-antibodies that are associated with different clinical features, which can be present in up to 70% of cases [9]. Muscle damage can be evaluated through muscle biopsy or MRI. The last, shows fatty infiltration (corresponding to areas of hyperintensity within muscles on T1-weighted images) and muscle edema (corresponding to areas of hyperintensity on short-tau-inversion-recovery sequences). DM muscle biopsy analysis shows perifascicular atrophy and perivascular inflammation, characterized by macrophages, B cells, and plasmacytoid dendritic cell infiltration. In the present case, the two measured auto-antibodies were negative, although other specific laboratory tests could not be performed due to limited resources. The muscle biopsy also was inconclusive, which is reported in up to 20% of inflammatory myopathies [10]. Nevertheless, the typical clinical features and MRI findings strongly support a diagnosis of statin-induced DM. Despite attempts to a definitive diagnosis, an autopsy studied was deferred by the patient’s family.

The present case also highlights the potential role of statins as triggers of immune system disease. It also emphasizes the need for more aggressive treatment and closer follow-up of cases without complete initial recovery. Contrary to the majority of cases reported so far, our report is characterized by very early development after initiating simvastatin therapy. Moreover, a malignant course ensued even after discontinuation of the offending agent and treatment with corticosteroids. Among the reasons for this could be the type of statin used. Lipophilic statins are more likely to enter non-hepatic cells such as myocytes and therefore may theoretically be more myotoxic. This may explain the large
number of case reports of myopathies induced by simvastatin and atorvastatin [11]. Although the exact mechanism of statins-induced DM is not completely known, genetic predisposition could also be involved. For example, several studies have demonstrated the disease is frequently related to variants in SLCO1B1, a gene regulating hepatic statin uptake. Because, the disease does not develop in the great majority of subjects with genetic predisposition, environmental triggers or additional genetic factors are also likely to have a casual role [12].

CONCLUSION
Although statins are currently the preferred pharmaceutical intervention for reducing the probability of CVD, statin-associated auto-immune myopathy exists as a rare side effect. When such diagnosis is suspected, immediate cessation of the agent and early institution of immunosuppressive therapy are critical. Nevertheless, rare cases can take a lethal course.

CONFLICT OF INTEREST STATEMENT
None declared.

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CONSENT
Written consent was provided by the patient’s relative.

GUARANTOR
Corresponding author (Dr D. Chemello).

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