Unexpected outcome (positive or negative) including adverse drug reactions

Simvastatin-induced dermatomyositis in a 50-year-old man

Inés Rania Zarea,¹ Imen Labbène,¹ Dalila Mrabet,² Hela Zribi,¹ Inès Chelly,³ Mohamed Zitouna,³ Mourad Mokni,¹ Slaheddine Sellami,² Amel Ben Osman¹

¹Department of Dermatology, La Rabta Hospital, Tunis, Tunisia;

²Department of Rheumatology, La Rabta Hospital, Tunis, Tunisia;

³Department of Pathology, La Rabta Hospital, Tunis, Tunisia

Correspondence to Dr Dalila Mrabet, mrabetdalila@yahoo.fr

Summary

Dermatomyositis (DM) is a rare inflammatory autoimmune disease for which an iatrogenic origin has been described in a few cases. The authors report a case of DM occurring after simvastatin intake.

A 50-year-old male sought medical attention for a photodistributed rash and considerable muscular weakness present for 3 months. One year earlier, simvastatin had been introduced. Serum creatine kinase levels were elevated. Histological examination of a muscle biopsy was consistent with a diagnosis of DM. Investigation for neoplasia and associated autoimmune disease proved negative. All clinical and laboratory abnormalities diminished corticosteroid therapy (1 mg/kg/day).

Case reports have suggested that lipid-lowering drugs, especially statins, could induce or reveal chronic muscle diseases. In statins myopathy, reduction of coenzyme Q has been discussed as a key mechanism. Our case of DM in a patient receiving simvastatin adds to the previous reported cases in the literature and highlights the potential role of statins as triggers of immune systemic diseases.

BACKGROUND

Dermatomyositis (DM) is a rare inflammatory autoimmune disease for which an iatrogenic origin is well known in the literature.^{1–4} The association between a lipid-lowering drug like statins and the development of a musculocutaneous syndrome has been previously reported.^{5–11}

We report a new case of statins induced DM and discuss the characteristics of this singular presentation through a review of the literature data.

CASE PRESENTATION

A 50-year-old man who sought medical attention for a 3-month history of photo-distributed rash, considerable muscular weakness and arthralgias presented to our department. He had been taking metformin and glibenclamide for diabetes mellitus revealed 4 years ago. One year earlier, simvastatin had been introduced following the discovery of dyslipidemia.

Clinical examination showed a characteristic rash with heliotropic colour and oedema affected his upper eyelids (figure 1A) and neckline. Gottron's papules were found overlying the extensor surfaces of the metacarpal and interphalangeal joints (figure 1B). He also had some nail fold telangiectasiae with papular purplish erythema and scaling on his elbows. The patient did not have fever, calcinosis, Raynaud's phenomenon, dyspnoea, oesophageal dysmotility and sclerodactyly. Muscle testing found evidence of proximal muscle weakness affecting the hip and shoulder girdles.

INVESTIGATIONS

Laboratory examinations showed raised levels of creatine kinase (714 UI: ×3.5 normal level) and lactate dehydrogenase (×1.5 normal level). Renal and hepatic

functions were normal. A lesional skin biopsy revealed interface dermatitis with vacuolar degeneration of basal keratinocytes, epidermal atrophy and interstitial mucin deposits in the dermis (figure 2). Direct immunofluorescence on skin biopsy was negative. Muscular biopsy was not performed. An electromyogram showed no evidence for myopathy. The antinuclear antibody test was positive at 1/1600. There were no antibodies to DNA or histone.

Investigations for an underlying neoplasm and associated autoimmune disease were negative.

TREATMENT AND OUTCOME

The simvastatin was discontinued. He was started on prednisone (1 mg/kg/day) and chloroquine (200 mg/day) with improvement of the clinical and laboratory abnormalities within 1 month.

DISCUSSION

Our patient developed a muscular and cutaneous clinical picture consistent with DM while taking simvastatin for hypercholesterolaemia. Rare but well-known complications of statin therapy include myopathy and rhabdomyolysis caused by non-inflammatory toxic or metabolic processes were reported.

The statins are competitive inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase activity. Myopathy occurs in 0.1–0.2% of patients receiving statins in clinical trials.^{1–4 12} Statin-induced myotoxicity, ranges in severity from myalgias to rhabdomyolysis resulting in renal failure and death. According to the American College of Cardiology/American Heart Association¹³ our patient presented statin myositis (muscle complaints with serum CK less more than 10 times of upper limit).

Figure 1 (A) A rash with heliotropic colour and oedema affected her upper eyelids. (B) Gottron's papules over the extensor surfaces of the hand. Nailfolds showed periungual erythema and telangiectatic changes.

Figure 2 Skin biopsy specimen showing interface dermatitis with vacuolar alteration of basal keratinocytes.

In a recent follow-up retrospective study of 37 patients, Sailler *et al*³ showed an increased exposure to statins in patients developing chronic muscle diseases. A literature review showed that cerivastatin (57%) was the most commonly implicated statin, followed by simvastatin (18%).²

Statin-induced DM is well known in the literature. While up to now 11 cases of statin associated DM (with

both skin and muscle involvement) have been reported. DM manifested between 2 months and up to 5 years after initiation of statin therapy. Remarkably, disease occurred after intake of first-generation (simvastatin, lovastatin and pravastatin) as well as of second-generation HMG-CoA reductase inhibitors (atorvastatin and fluvastatin). Statin exposure may increase by three fold the risk of developing an inflammatory myopathy after the age of 50.

There have been five previously reported cases of DM syndrome in patients receiving this type of cholesterol-lowering agents (simvastatin).^{7–11} Three of the reported cases included both skin and muscle involvement. One fatal outcome was reported due to DM-associated lung fibrosis.⁸ DM manifested between 6 months up to several years after initiation of simvastatin therapy (1 year in our case) and included heliotrope and photodistributed skin rash with proximal muscle weakness in three cases. As in our patient antinuclear antibodies (AAN=1/1600) were positive in two cases, negative in one case and unspecified in one case.

Our case of simvastatin-associated DM adds to the previous reported cases in the literature and highlights the potential role of statins as triggers of immune systemic diseases. An increasing number of reports suggests that statins may also trigger other autoimmune reactions resulting in systemic or subacute cutaneous lupus erythematosus and systemic sclerosis.⁶

The pathomechanism of statin-induced DM is not yet well understood. It has been speculated that statins may under certain conditions promote cellular apoptosis, which subsequently results in the release of nuclear antigens from dying cells. As a consequence, autoimmunity may arise and lead to disease manifestation. Prolonged exposure to statins may also increase HLA class I expression by myocytes, promote chronic exposure of previously hidden antigens following myocyte injury and/or induce a TH2 type immune response leading to DM/PM.^{1 2} All these proposed mechanisms could not be tested for our patient.

The risk of myopathy with statins use can be exacerbated by several factors, including compromised hepatic and renal function, hypothyroidism, diabetes mellitus¹² as in our patient. These effects are, in part, due to an over-dosing of drugs simultaneously oxidised by cytochrome P450 3A4 (fibrates, CYP3A4 inhibitors including cyclosporin, erythromycin, azole antifungals, calcium channel blockers and antiretrovirals such as ritonavir).^{4 14} This may be due also to the additive effect of the demonstrated statin mitochondrial toxicity in all users and, to a greater degree, in vulnerable individuals.¹² Glibenclamide and metformin used in our case are not reported to inhibit metabolic pathways of statins.

Statins may also trigger the clinical expression of latent genetic neuromuscular disorders by adding their own toxic effects to latent abnormalities in muscle metabolism or structure.¹⁴

Regarding the large-scale prescription of HMG-CoA reductase inhibitors, the risk for developing statin-associated DM appears to be rather low. Nevertheless, statins should be added to the list of drugs which are capable of eliciting DM. DM can be considered as a severe adverse

reaction to statins although a distinct casual link cannot be definitely established. In contrast to other toxic effects, drug-induced autoimmune responses may persist despite cessation of the responsible compound, and immunosuppressive therapy is often required.^{7–11} Our patient was treated with prednisone and chloroquine. One month later, cutaneous lesions had almost completely cleared.

Apart from one fatal outcome due to DM-associated lung fibrosis, statin-associated DM shows a relatively benign course, as in our patient. However, most cases required systemic treatment with glucocorticoids and were characterised by a slow recovery.

Learning points

- ▶ DM is a rare inflammatory autoimmune disease for which an iatrogenic origin has been described in a few cases.
- ▶ Complications of statin therapy include myopathy and rhabdomyolysis.
- ▶ Statin-associated DM shows a relatively benign course.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. **Hamilton-Craig I.** Statin-associated myopathy. *Med J Aust* 2001;**175**:486–9.
2. **Thompson PD,** Clarkson P, Karas RH. Statin-associated myopathy. *JAMA* 2003;**289**:1681–90.
3. **Sailler L,** Pereira C, Bagheri A, *et al.* Increased exposure to statins in patients developing chronic muscle diseases: a 2-year retrospective study. *Ann Rheum Dis* 2008;**67**:614–9.
4. **Klopstock T.** Drug-induced myopathies. *Curr Opin Neurol* 2008;**21**:590–5.
5. **Seidler AM,** Gottlieb AB. Dermatomyositis induced by drug therapy: a review of case reports. *J Am Acad Dermatol* 2008;**59**:872–80.
6. **Noël B.** Lupus erythematosus and other autoimmune diseases related to statin therapy: a systematic review. *J Eur Acad Dermatol Venerol* 2007;**21**:17–24.
7. **Khattak FH,** Morris IM, Branford WA. Simvastatin-associated dermatomyositis. *Br J Rheumatol* 1994;**33**:199.
8. **Hill C,** Zeitz C, Kirkham B. Dermatomyositis with lung involvement in a patient treated with simvastatin. *Aust N Z J Med* 1995;**25**:745–6.
9. **Vasconcelos OM,** Campbell WW. Dermatomyositis-like syndrome and HMG-CoA reductase inhibitor (statin) intake. *Muscle Nerve* 2004;**30**:803–7.
10. **Inhoff O,** Peitsch WK, Paredes BE, *et al.* Simvastatin-induced amyopathic dermatomyositis. *Br J Dermatol* 2009;**161**:206–8.
11. **Rasch A,** Schimmer M, Sander CA. Simvastatin-induced dermatomyositis. *Hautarzt* 2009;**60**:489–93.
12. **Golomb BA,** Evans MA. Statin adverse effects: a review of the literature and evidence for a mitochondrial mechanism. *Am J Cardiovasc Drugs* 2008;**8**:373–418.
13. **Pasternak RC,** Smith SC Jr, Bairey-Merz CN, *et al.* ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *J Am Coll Cardiol* 2002;**40**:567–72.
14. **Vladutiu GD.** Genetic predisposition to statin myopathy. *Curr Opin Rheumatol* 2008;**20**:648–55.

This pdf has been created automatically from the final edited text and images.

Copyright 2011 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Zaraa IR, Labbène I, Mrabet D, Zribi H, Chelly I, Zitouna M, Mokni M, Sellami S, Osman AB. Simvastatin-induced dermatomyositis in a 50-year-old man. *BMJ Case Reports* 2011;10.1136/bcr.02.2011.3832, date of publication

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow