

***Pityriasis lichenoides chronica* Associated with Use of HMG-CoA Reductase Inhibitors**

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ABSTRACT

Herein, we present three cases of Pityriasis lichenoides chronica (PLC) in patients who developed the rash after use of 3-hydroxy-3-methyl-glutaryl-Coenzyme A (HMG-CoA) reductase inhibitors. The patients had complete resolution after standard treatment by dermatologists and withdrawal of the offending agents. In one case, the patient had a previous episode of a similar rash that occurred with HMG-CoA reductase inhibitors use many years previously. Pityriasis lichenoides chronica is a condition of unknown aetiology. Several agents have been associated with its presentation. We postulate HMG-CoA reductase inhibition in skin presents a final common pathway for the presentation of PLC in select patients.

Keywords: Erythematous rash, HMG-CoA reductase inhibitors, *Pityriasis lichenoides chronica*, statins

***Pitiriasis liquenoide crónica* Asociada con el Uso de Inhibidores de la Reductasa de HMG-CoA**

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RESUMEN

Se presentan tres casos de pitiriasis liquenoide crónica (PLC) en pacientes que desarrollaron una erupción tras el uso de inhibidores de la reductasa de la hidroximetilglutaril-coenzima A (HMG-CoA). Los pacientes tuvieron resolución completa después del tratamiento estándar dado por los dermatólogos, y la suspensión de los agentes ofensivos. En un caso, el paciente tuvo un episodio de una erupción similar anterior, que ocurrió debido al uso de inhibidores de la reductasa de HMG-CoA muchos años atrás. La pitiriasis liquenoide crónica es una condición de etiología desconocida. Varios agentes han sido asociados con su manifestación. Se postula que la inhibición de la reductasa de HMG-CoA presenta un camino final común para la manifestación de PLC en determinados pacientes.

Palabras claves: Erupción eritematosa, inhibidores de la reductasa de HMG-CoA, *Pitiriasis liquenoide crónica*, estatina

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INTRODUCTION

The clinical indications for statin use are expanding. Liver and muscle side effects are the most commonly reported complications with this class of drugs (1). Skin lesions are rare but well-documented side effects associated with these medications. We anticipate that the increased use of statins may result in an increased frequency of dermatological

lesions in the clinical side effect profile of these drugs. We describe three cases of *Pityriasis lichenoides chronica* (PLC) associated with statin use.

CASE REPORT

Case 1: A 62-year old male with Type 2 diabetes mellitus presented to clinic with symptoms suggestive of angina. Medications at presentation were gliclazide 30 milligrams (mg) orally twice daily and metformin 500 mg orally three times daily. He was found to be hypertensive and a clinical diagnosis of ischaemic heart disease was made. The patient was started on diltiazem slow release formulation 90 mg orally once daily and simvastatin 20 mg orally once daily, but subsequently defaulted from follow-up.

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Eight years following the first visit he had a non ST segment elevation myocardial infarction (NSTEMI) for which conservative management was instituted, as follows: atenolol 5 mg orally once daily, pravastatin 40 mg orally once daily, ramipril 2.5 mg orally once daily, clopidogrel 75 mg orally once daily and aspirin 150 mg orally once daily, along with his previous medications for diabetes. Approximately one year afterwards, the patient developed a generalized papular rash on an erythematous base located on the limbs on the background of dry skin. He was referred to a dermatologist who biopsied the lesion. Histopathology report confirmed the diagnosis of PLC. Treatment was started with topical moisturizers, antibiotics and steroids with significant improvement. The patient then recalled having a similar rash that occurred eight years previously while using simvastatin. Pravastatin was discontinued with complete resolution of the skin rash after two months. Patient refused rechallenge with 3-hydroxy-3-methyl-glutaryl-Coenzyme A (HMG-CoA) reductase inhibitors.

Case 2: This was a 70-year old obese male with hypertension for four years and acute left ventricular failure (LVF) one year prior to presentation. He was diagnosed with ischaemic heart disease during investigation for his LVF. The patient was started on pravastatin 40 mg daily in addition to his previous medications: aspirin, trimetazidine, losartan and furosemide. Approximately three years after initial evaluation, the patient presented with a rash and was subsequently referred for further management to the dermatologist. The dermatologist found a maculopapular squamous rash on the entire trunk and the limbs. Some of the lesions were hyperpigmented, others were of a violaceous colour. Many of the papules were surmounted by a single scale. He was diagnosed clinically with PLC and started with 1/10 strength dermivate cream with added glycerine and urea as emollients. His condition improved but new lesions continued to appear. The decision was made to obtain a skin biopsy which confirmed the diagnosis of PLC. Pravastatin treatment was discontinued with resolution of his rash less than two months afterwards.

Case 3: A 79-year old female with a four-year history of hypertension and three-year history of hypercholesterolaemia was noted to have an asymptomatic cardiac murmur by her general practitioner and sent to the cardiologist for further review. The patient was initially started on pravastatin for three months with inadequate control and changed to rosuvastatin 20 mg daily. Other medications included felodipine 10 mg, indapamide 1.5 mg and aspirin 81 mg daily, respectively. The patient was noted to have a rash that was thought to be *Pityriasis versicolor*. The rash persisted and a referral to a dermatologist was requested. The dermatologist (same as in case one) described the rash as small papular lesions on dry skin and diagnosed the patient with PLC.

HMG-CoA reductase inhibitors were discontinued with improvement in the rash. The patient refused a rechallenge.

DISCUSSION

Pityriasis lichenoides (PL) is part of a constellation of acquired inflammatory skin disorders that include *Pityriasis lichenoides et varioliformis acuta* (PLEVA), febrile ulceronecrosis Mucha-Habermann disease (a subtype of PLEVA) and PLC (2, 3). The incidence and prevalence of PL are still unclear. It may present in any individual of any age, ethnicity and geographic area (1).

The diagnosis and differentiation of PL variants is a clinical one. *Pityriasis lichenoides chronica* is considered the more common and subtle form of PL (4). It is distinguished by gradually developing small, dim erythematous-to-brown flattened maculopapules with fine centrally attached shiny scales (5). *Pityriasis lichenoides chronica* is distributed over the trunk, buttocks, and proximal extremities (2). It may present as hypopigmented papules in black or dark skinned patients (2, 6). A skin biopsy and subsequent histopathologic examination is a confirmatory tool (1).

The exact pathogenic mechanism for *Pityriasis lichenoides* is unknown, numerous implications and associations have been made that center around an inflammatory reaction (1, 2). One aetiologic hypothesis is that it is a form of atypical immune response to a foreign agent in genetically susceptible individuals (2, 4).

HMG-CoA reductase inhibitors suppress cholesterol synthesis in the liver. The human skin contains a lipid bilayer in the stratum corneum that is composed of ceramides, free fatty acids and cholesterol (7). It contains all the enzymes for a *de novo* cholesterol biosynthesis (8). Therefore drugs such as HMG-CoA that interfere with cholesterol biosynthesis may have effects on cutaneous barrier function (1). They reduce epidermal cholesterol synthesis with a late compensatory upregulation of fatty acid synthesis. These biochemical changes may result in increased transepidermal water loss and scaling of the skin (7, 9).

In summary, *Pityriasis lichenoides chronica* is a benign condition that has clinical importance because it is part of the same spectrum of disease as febrile ulceronecrosis Mucha-Habermann disease, which has been associated with complications such as bacteraemia and sepsis. Occasional cases have shown transformation to cutaneous lymphoma.

With the increasing use of HMG-CoA reductase inhibitors in patients with cardiovascular disease, we can possibly expect a rise in the incidence of complications related to their use. More attention should be placed on the effect of statins on other organs such as the skin and the long term complications these effects will have. The changes in the stratum corneum lipids may be the initiating triggering factor for the inflammatory reaction seen in the other associated causes of PLC.

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