Atorvastatin-induced Lupus Erythematosus Tumidus: A Case Report and Literature Review

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ABSTRACT Lupus erythematosus tumidus (LET) is a rare photosensitive skin disease classified as a separate subtype of cutaneous lupus erythematosus. Clinically, it is characterized by erythematous plaques on sun-exposed areas. Typical histopathological findings are perivascular and periadnexal lymphohistiocytic infiltrates and prominent mucin deposition in the dermis. Treatment is based on photoprotection, topical corticosteroids, and antimalarial drugs. The exact pathogenesis of the disease is unknown. Drugs are considered a minor risk factor for the development of LET. We present a case of a 56-year-old woman who developed LET after starting treatment with atorvastatin. We describe her clinical course and review the literature concerning the cutaneous adverse reactions induced by statin drugs. To our knowledge, this is the first case of statin-induced LET. We conclude that statins can induce LET and that it is important for clinicians to be aware of this potential adverse effect associated with statins.

KEY WORDS: statin, cutaneous lupus erythematosus, intermittent cutaneous lupus, lupus erythematosus tumidus

INTRODUCTION

Lupus erythematosus tumidus (LET) is an uncommon photosensitive skin disease that is characterized by indurated, succulent, edematous, erythematous plaques (1). The term LET was introduced by Erich Hoffmann in 1909 (2). Since the first reported case of LET, several reports and case series have been published to date, but it was only in recent decades that research on the clinical and histological aspects of the disease has been performed (1,3-5). LET was previously not considered a separate entity and was subclassified as a form of chronic cutaneous lupus erythematosus, together with discoid lupus erythematosus, chilblain lupus erythematosus, and lupus erythematosus panniculitis/profundus. Kuhn *et al*. presented the clinical and histological features of LET and suggested that LET should be considered a distinct entity and be part of the Duesseldorf classification as intermittent CLE (ICLE) (6,7). The most important characteristics that distinguish LET from other types of cutaneous lupus erythematosus (CLE) are extreme photosensitivity, good response to treatment with antimalarial drugs, and distinctive histopathologic findings (8,9). The exact pathogenesis of LET is unknown (10). Drugs are considered a minor risk factor for the development of LET, and as of yet there is no report of LET after treatment with statin drugs (6). We present a case of a 56-year-old woman with LET induced with atorvastatin and review the literature concerning cutaneous adverse reactions induced with statin drugs.

CASE REPORT

A 56-year-old woman presented with a 2-month history of multiple mildly itchy non-scaly erythematous plaques on her face and upper back. The

eruption appeared one month after starting treatment with atorvastatin. The patient had no previous history of skin disease or photosensitivity. Other than atorvastatin, the patient was taking vitamin D, tiotropium bromide, fluticasone furoate/vilanterol, and levothyroxine. Physical examination revealed several erythematous plaques on the face and upper back, ranging from 3 mm to 30 mm in diameter (Figure 1).

Routine laboratory tests including complete blood count, chemistry, and immunochemistry (alfa-fetoprotein, CEA, CA19-9, CA-15-3, CA-125), and serum protein electrophoresis were within normal limits. The only pathological values were a high erythrocyte sedimentation rate (76 mm/h, normal <28 mm/h) and serum beta2-microglobulin concentration (3.19 mg/L, normal <2.5 mg/L). A complete autoantibody screening panel revealed positive antinuclear antibodies (ANA), H+, titer 1:160 negative. Extractable nuclear antigen (ENA), antidouble-stranded DNA (ds-DNA) autoantibody, anti-Ro/La antibody, anti-Smith (Sm) antibody, anti-RNP antibody, anti-Jo1 antibody, anti-Scl-70 antibody tests were negative.

We performed a 4 mm punch biopsy of one of the back lesions. Pathohistological findings revealed moderate periadnexal and perivascular interstitial lymphoplasmacytic infiltrate accompanied by mucin deposition in the dermis. Immunofluorescence examination showed discrete focal granular deposits of IgM and C3 in the walls of small vessels and IgG and IgM along the dermoepidermal border (Figure 2, Figure 3). Based on the clinical characteristics and pathohistological findings, a diagnosis of LET was established.

The patient discontinued treatment with atorvastatin and started treatment with mometasone cream and external photoprotection. After a few weeks, the skin changes disappeared and the patient has not had a relapse to date.

DISCUSSION

LET is a rare inflammatory skin disorder that is now considered a separate subtype of CLE with a benign, intermittent clinical course, and is only rarely associated with systemic lupus erythematosus (SLE) (6). In contrast to other CLE subtypes that predominantly affect women, LET has been reported to be present equally in women and men or with a slight predominance in women (6,10). LET can affect people of all ages, including children. Kuhn *et al*. reported that the mean age at onset of the disease in 40 patients with LET was 36.4 years (1). Currently, there are no data in the literature regarding the prevalence and incidence of LET (8).

There is no clear understanding of the pathogenesis of LET. Several factors may contribute to the development of LET, including UV irradiation, dysregulation of the immune system, reduced clearance of apoptotic cells, and externalized autoantigens (11).

LET clinically presents as succulent, edematous, urticaria-like, single or multiple plaques with a bright

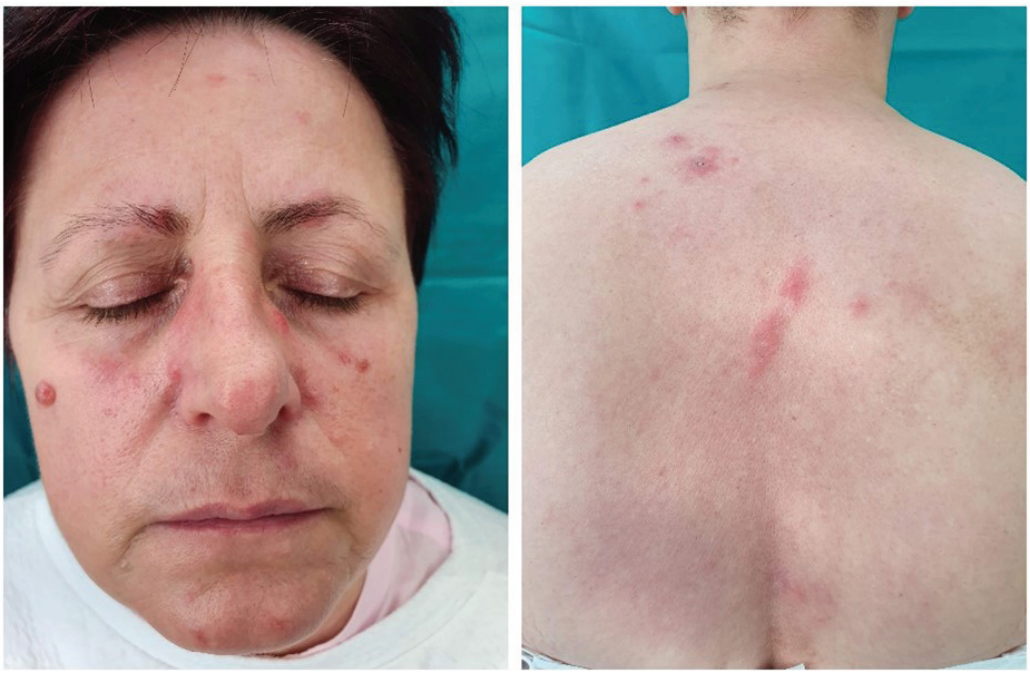

Figure 1. Erythematous plaques on the face and upper back.

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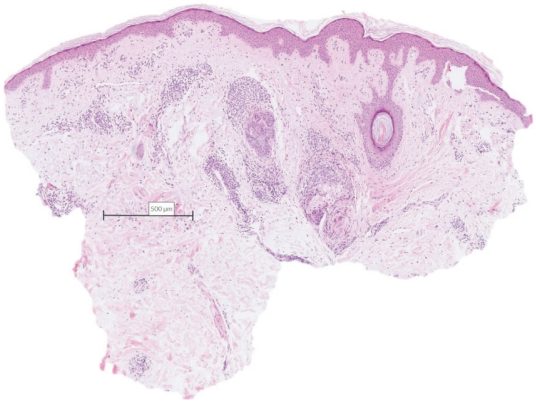

Figure 2. Punch biopsy of the skin with mild to moderate superficial and deep perivascular and periadnexal mononuclear cell infiltrate. Hematoxylin and eosin stain.

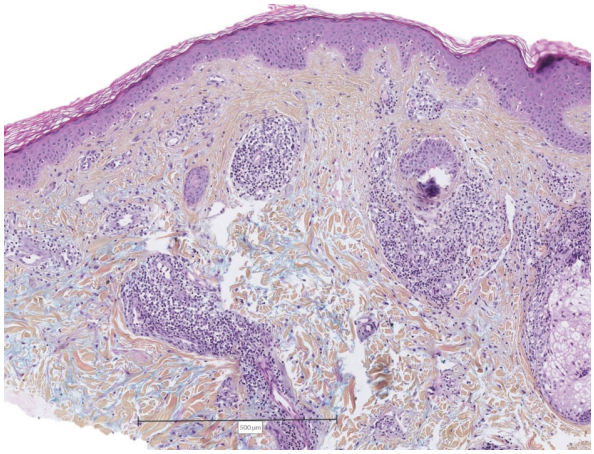

Figure 3. Higher magnification depicting deposition of mucin in the dermis. Also note the presence of moderately intense perivascular and periadnexal mononuclear infiltrate, composed mostly of lymphocytes. There is no interface tissue reaction. Kreyberg stain.

reddish or violaceous, smooth surface without the involvement of the epidermis (1). LET lesions usually have a swollen appearance and sharply limited borders, and the lesions can sometimes coalesce in the periphery, producing a gyrate configuration, or can swell in the periphery and be flat in the center (12). Skin lesions appear on sun-exposed areas, such as the face, upper back, V-area of the neck, extensor aspects of the arms, scalp, and shoulders. The knuckles, inner aspect of the arms, axillae, and skin below the waist are usually unaffected. Lesions heal without scaring or postinflammatory hyper- or hypopigmentation, and therefore LET does not result in chronic skin damage (6).

A skin biopsy with the use of a hematoxylin and eosin stain is necessary to confirm the diagnosis of LET (6). Histological findings that support the diagnosis of LET are superficial and deep perivascular and periadnexal lymphocytic infiltration and prominent mucinous depositions. Important features of other subtypes of CLE, such as atrophy and follicular plugging of the epidermis, vacuolar degeneration of the dermoepidermal junction, or basement membrane thickening, are absent or show minimal and focal alterations. Direct immunofluorescence is typically negative in patients with LET, but immunoglobulin or complement components can be found at the dermoepidermal junction in some cases (13). Immunohistochemical findings characteristic of LET are predominance of T-lymphocytes and the predominance of CD4 over CD8 lymphocytes in the inflammatory infiltrate (14). Standardized photoprovocation can be performed in atypical cases to support the diagnosis of LET. LET is a highly photosensitive disease and is considered the most photosensitive form of CLE. It is characterized by late onset of photosensitivity, as lesions appear more than >48 hours after UV exposure and last for several days to several weeks (6). Due to a rare but possible association with SLE, patients should be questioned for potential symptoms from other systems and be appropriately physically examined. Evaluation of full blood count, urine analysis for proteinuria and blood cell cast, and complete autoantibody screening is suggested (6). Antinuclear (ANA), anti-ENA, anti-SM, anti-Ro, anti-La, and anti-DNA antibodies are usually negative in patients with LET (15). The main differential diagnoses of LET are reticular erythematous mucinosis (REM), polymorphic light eruption (PLE), and Jessner's lymphocytic infiltration of the skin (LIS) (6).

Since LET is highly photosensitive, patients should avoid sun exposure and use photo-resistant clothing and a broad-spectrum sunscreen with a high protection factor. In certain cases, sun protection and moderate-potency topical corticosteroids are sufficient (9). Second-line topical treatments are topical calcineurin inhibitors (pimecrolimus 1% cream or tacrolimus 0.1% ointment) (16).

However, most patients require treatment with antimalarial drugs (hydroxychloroquine or chloroquine) that rapidly and effectively improve the skin lesions, and systemic treatment with other drugs, such as systemic corticosteroids, immunosuppressants or immunomodulating agents (dapsone, methotrexate, mycophenolate mofetil, etc.), is therefore rarely needed (7,18). Smoking negatively influences the course of the disease and correlates with a worse response to antimalarial drugs, and patients should therefore be strongly advised to stop smoking before starting the treatment (16).

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Table 1. Summary of cutaneous adverse reactions associated with statins

Cutaneous drug reaction	Culprit drug	Reference
Actinic dermatitis (chronic)	simvastatin	(17,18)
Acute generalized exanthematous pustulosis	simvastatin	(19)
Alopecia	atorvastatin	(20)
Anaphylaxis	atorvastatin	(21,22)
Cheilitis	simvastatin	(23)
Chronic urticaria	atorvastatin	(24)
Dermographism	atorvastatin	(25)
Dermatomyositis	atorvastatin	(26-28)
Drug reaction with eosinophilia and systemic symptoms	atorvastatin, rosuvastatin	(29-31)
Eczema	lovastatin, simvastatin, pravastatin	(32-35)
Erythema multiforme	simvastatin, pravastatin	(36)
Eosinophilic fasciitis	simvastatin, atorvastatin	(37,38)
Henoch-Schonline purpura	rosuvastatin	(39)
Ichtyosis	pravastatin, pitavastatin	(40,41)
Lichen planus pemphigoides	simvastatin	(42)
Cutaneous drug reaction	**Culprit drug**	**Reference**
Lichenoid drug eruption	simvastatin, pravastatin, fluvastatin, lovastatin	(43-48)
Linear IgA bullous dermatosis	atorvastatin	(49)
Pemphigus erythematosus	atorvastatin	(50)
Photosensitivity	atorvastatin, simvastatin	(51-54)
Pityriasis lichenoides chronica	pravastatin	(55)
Pityriasis lichenoides-like drug reaction	atorvastatin	(56)
Pityriasis rubra pilaris	simvastatin	(57)
Porphyria cutanea tarda	simvastatin, pravastatin	(58)
Psoriasis worsening	atorvastatin	(59)
Purpura	rosuvastatin, pravastatin	(60,61)
Pustular eruption	simvastatin	(62)
Subacute lupus erythematous	simvastatin	(63,64)
Toxic epidermal necrolysis	atorvastatin	(65)
Skin ulcers	pravastatin	(66)
Oral ulcers	rosuvastatin	(67)
Urticarial vasculitis	simvastatin	(68)

The prognosis of patients with LET is normally better than in those with other forms of CLE, as LET is rarely associated with SLE, has a benign nature, and has an intermittent course with relapsing lesions after disease-free periods or with long-term remission. Furthermore, skin lesions heal without scarring, dyspigmentation, or lipoatrophy (9).

Statins, or 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, have been widely used for years to prevent hypercholesterolemia, but their adverse effects on the skin have been well-documented (Table 1) (17-68). To date, there has been no report of LET caused by statin therapy. It has been reported that several drugs can cause LET (69-78). The pathogenetic mechanism of drug-induced LET is unknown. There are two proposed pathogenic mechanisms. Known to be proapoptotic agents, statin drugs can trigger cell apoptosis and the subsequent exposure of autologous DNA (79,80). It has been hypothesized that certain peptides bind to autologous DNA and form complexes that activate the plasmacytoid dendritic cells, resulting in the production of type I interferon, which plays a key role in the etiology and pathogenesis of lupus (15,81).

Statins can also cause photosensitivity, as cases of phototoxic reactions have been reported after taking atorvastatin (82).

Our patient developed clinically and histologically confirmed LET possibly correlated with atorvastatin treatment. We assume that LET was statin-in-

duced, since the onset of the conditions was closely related to the time since the drug was consumed and because of its normalization after discontinuing the statin intake. Phototests were not preformed, since the lesions disappeared after discontinuation of drug intake.

The patient responded well to the treatment and has not had a relapse to date.

CONCLUSION

LET is a relatively rare disease. Although drug inductions are considered a minor risk factor for the development of LET, there have been several reports associating various medications with the disease. In this case report, we present the first known case of LET induced with a statin. We emphasize the importance of careful clinical examination followed by histopathological examination, as LET is thought to be underdiagnosed, and more reported cases would facilitate the research and improvement of the diagnosis and treatment of this disease.

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