Drug-induced Subacute Cutaneous Lupus Erythematosus Caused by a Topical Beta Blocker – Timolol

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ABSTRACT Drug-induced lupus erythematosus (DI-LE) is an autoimmune condition secondary to a recent pharmacological intervention. There are no established specific diagnostic criteria for DI-LE, and the disease is recognized based on the medical history of the patient. Typically, the onset is closely related to a recent drug exposure, and the disease terminates after discontinuation of the inducing factor. The most frequent form of DI-LE is drug-induced subacute cutaneous lupus erythematosus (DI-SCLE). There has been an increasing number of drugs which are suspected to provoke SCLE lesions. Previously, systemic beta-blockers (antiarrhythmics and antihypertensives) were shown to be inducing factors of SCLE, however data regarding its topical usage are lacking in the literature. We present the case of a 78-year-old woman who developed annular polycyclic erythema in sun-exposed areas of the skin, four weeks after an initiation of topical timolol treatment of glaucoma. A resolution of cutaneous manifestations within only a few weeks after a cessation of the agent confirmed a clinical suspicion of drug-induced SCLE.

KEY WORDS: subacute cutaneous lupus erythematosus, topical, timolol, beta blocker, drug-induced

INTRODUCTION

Drug-induced lupus erythematosus (DI-LE) is an autoimmune condition secondary to a recent pharmacological intervention. There are no established specific diagnostic criteria for DI-LE, and the disease is recognized based on the medical history of the patient. Typically, the onset is closely related to a recent drug exposure and the disease terminates after discontinuation of the inducing factor. DI-LE, likewise an idiopathic form of lupus erythematosus, may manifest as a systemic or cutaneous disease (1,2). However, drugs can be inducing factors for all clinical variants, the most frequent form is drug-induced subacute cutaneous lupus erythematosus (DI-SCLE). Clinically, annular polycyclic or papulosquamous lesions develop in sun-exposed areas of the skin soon after a new pharmacological intervention (2,3). We present a case of SCLE which developed four weeks after an initiation of topical timolol treatment of glaucoma.

CASE REPORT

A 78-year-old woman was admitted to our Dermatology Department due erythematous skin lesions

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Table 1. Drugs identified as agents provoking systemic lupus erythematosus (SCLE)

SYSTEMIC LUPUS ERYTHEMATOSUS	
Hydralazine, procainamide, isoniazid and minocycline	
SUBACUTE CUTANEOUS LUPUS ERYTHEMATOSUS	
Antihypertensives – about 34%	Diuretics – Hydrochorothiazide Calcium channel blockers – Diltiazem, verapamil Oral beta blockers – Oxprenolol
Antifungals – about 25%	Terbinafine
Others	Chemotherapeutics Antihistamines Immunomodulators Proton pump inhibitors Nonsteroidal anti-inflammatory drugs and other
CHRONIC CUTANEOUS LUPUS ERYTHEMATOSUS	
Fluorouracile agents, Nonsteroidal anti-inflammatory drugs, TNF-alpha antagonists	

(Figure 1). Cutaneous findings were located predominantly in sun-exposed areas and had a tendency to form annular, polycyclic shapes. Retrospectively, the lesions started to appear one-month before on the skin of the lower neck area (Figure 2), extending to the back and upper extremities. The skin under underwear was intact (Figure 3).

Initially, cutaneous pathologies were suggestive of photosensitivity reaction. They did not respond well to antihistamines and topical corticosteroids. There was a suspicion of allergy to drugs prescribed due to the patient's comorbidities, but no systemic agents had been modified over the previous months. The patient was receiving antihypertensive drugs (losartan, nebivolol), acetylsalicylic acid, metformin due to type 2 diabetes mellitus, and lipid-lowering therapy. Interestingly, four weeks earlier the patient had commenced topical treatment with timolol for glaucoma. It was not initially suspected as a causative factor, particularly due to a lack of periorbital cutaneous manifestations.

There was only a mild decrease of white blood count – 3.49 G/L (N: 4.00-10.00 G/L) in laboratory tests. An assay of antinuclear antibodies revealed a presence of anti-Ro/SSA. Anti-dsDNA or anti-histone antibodies were not identified. A skin biopsy taken from the neck showed a fair hydropic degeneration of the basilar epithelial layer and a prominent edema of the dermis. Both anti-Ro/SSA antibodies and the histopathology were suggestive for SCLE.

Chloroquine was contraindicated because the patient presented retinopathy in fundus examination caused by long-term diabetes. Systemic corticosteroids were also undesirable due to diabetes. The Naranjo algorithm determined the probable adverse drug reaction was the recently-introduced drug, and the decision to cease topical timolol was made. It was switched to bimatoprost. The therapy with antihistaminic and topical corticosteroids was

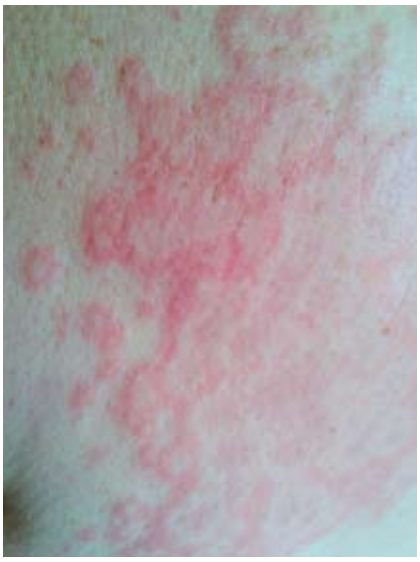

Figure 1. Erythematous lesions with a tendency to form annular polycyclic shapes.

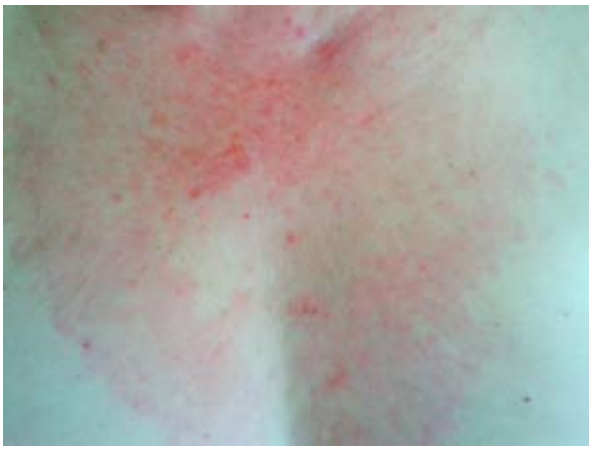

Figure 2. Neck area affected by lesions.

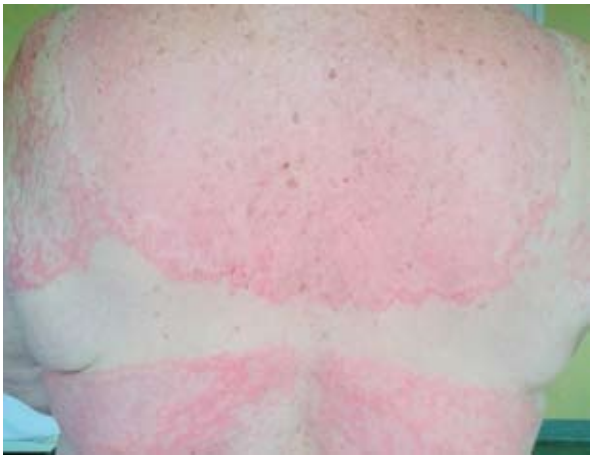

Figure 3. Extended lesions presenting on the back with characteristic spared areas.

continued. Soon after the discontinuation of topical timolol, cutaneous lesions gradually started to resolve, and within four weeks only slight erythema was noticeable.

DISCUSSION

A development of drug-induced systemic lupus erythematosus was first reported in 1952 after an exposure to hydralazine. Its subacute cutaneous variant was later described in 1985 in association with hydrochlorthiazde (4,6). The list of drugs identified to be inducing factors for LE has been expanded since (Table 1) (1,4).

Typically, DI-LE affects women (about 75% of cases), predominantly in the sixth decade of life. Cutaneous manifestations usually occur in sun-exposed areas, preferentially on the upper neck, shoulders, and the upper extremities (3,4). It is assumed that a photosensitive reaction is triggered by a drug as an isomorphic response; however, it occurs only in predisposed individuals. Increased risk of photosensitivity is a characteristic feature of most drugs which are suspected to be inducing factors for SCLE. Conceivably, a concomitant existence of other factors can enhance photosensitive response to some drugs. Those could be factors other than drugs photosensitizing chemicals, cigarettes, or infections; however, none of them were reported in our patient (2,4).

The delay between starting with timolol exposure and the development of skin lesions was approximately four weeks. In the literature, the mean time of latency varies from only 3 days to as much as 11 years. The resolution of cutaneous findings may last from only 1 week up to several months after the withdrawal of the inducing drug (4).

To the best of our knowledge, there are no case reports of subacute cutaneous lupus erythematosus induced by use of ophthalmic drops available in the English literature. Induction of systemic LE was previously reported by Zamber *et al.* A male patient developed fever, malaise, pleurisy, and recurrent sterile pleural effusions while taking no medication other than timolol. Anti-histone antibodies were positive, while antibodies to native DNA were absent. A discontinuation of ophthalmic treatment promptly improved the symptoms as in case of our patient (7).

Topical timolol, like systemic drugs, generated anti-Ro/SSA antibodies. Anti-histone antibodies are rarely found (3). Homberg *et al.* classified timolol as a weak inducer of iatrogenic lupus when compared with major drugs: procainamide, high doses of hydralazine, and D-penicillamine (8). However, topical beta-blockers are suspected of increasing antinuclear antibodies in the patients sera. (9)

Almost complete resolution of skin lesions after four weeks strongly suggests a causative role of timolol for the development of cutaneous lupus in our patient. It proves that the most effective management in DI-LE is a discontinuation of the inducing drug without the need for additional immunosuppressive treatment (1,4).

CONCLUSION

Our case report emphasizes that DI-LE is also associated with the use of topical agents even without oral intake. It is always important to consider all pharmacological interventions, not necessarily only systemic ones, which enables the elimination of the triggering factor without immunosuppressive treatment.

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