Subacute cutaneous lupus erythematosus in a patient with Sjögren's Syndrome taking terbinafine for onychomycosis

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ABSTRACT

We report the case of a 40-year old woman followed at our Rheumatology department for a 14-year history of a relatively well controlled Sjögren's Syndrome who developed, for the first time in life, lesions suggestive of subacute cutaneous lupus erythematosus, nine weeks after taking oral terbinafine prescribed for onychomycosis. She denied additional symptoms, namely systemic manifestations, and no other clinical finding besides cutaneous lesions were detected. No laboratory findings were in favour of a flare of her connective tissue disease. Here we explore the possibility of terbinafine-induced subacute cutaneous lupus erythematosus in the context of previous autoimmunity. This clinical case highlights the importance of avoiding the prescription of terbinafine in this kind of patients.

Keywords: Drug-induced subacute cutaneous lupus erythematosus; subacute cutaneous lupus erythematosus; Sjögren's Syndrome

INTRODUCTION

Drug induced lupus erythematosus (DILE), also reported in literature as drug-induced lupus, drug-related lupus, lupus-like syndrome or lupus erythematosus medicamentosus, is defined by the presence of clinical manifestations and immunopathological serum findings similar to those of idiopathic lupus, but temporally related to continuous exposure to a drug (from one month to as over a decade) that resolves after its discontinuation[1–3]. Since the first description in 1945, associated with sulfadiazine, more than 80 drugs have been reported to induce DILE[1]. Pathogenesis of DILE remained not fully understood. It has been proposed that drugs could act through direct mechanisms, operating along the same pathways as those employed for the obtention of the therapeutic effect (as for anti-TNF), or through indirect mechanisms, by employing reactive metabolites (as for procainamide, isoniazid, hydralazine) and by inhibition of DNA methylation (as for procainamide)[2]. As in idiopathic lupus, DILE can be divided into three types: drug induced systemic lupus erythematosus (DI-SLE), drug induced subacute cutaneous lupus erythematosus (SI-SCLE) and drug induced chronic cutaneous lupus erythematosus (DI-CCLE)[1–3]. DI-SCLE, described for the first time in 1985 after exposition to hydrochlorothiazide, is the most common form of DILE and some authors considered it under-recognized[1,4,5]. Here we report the case of a patient with a 14-year history of Sjögren's Syndrome (SjS), with positive anti-SSA, who developed cutaneous lesions highly suggestive of SCLE, nine weeks after initiation of oral terbinafine for onychomycosis.

CASE REPORT

A 40 year-old female, with a history of asthma and Guillain-Barré Syndrome at the age of 12, was followed at our Centre for a primary SjS, diagnosed at 26 years-old, given the presence of suggestive clinical manifestations (xerophthalmia, vaginal dryness, fatigue, recurrent episodes of palpable purpura), objective signs of ocular dryness and salivary gland involvement (positive Schirmer's test, salivary scintigraphy with moderate impairment of uptake and excretion of the parotid and severe impairment of the function of the submaxillary glands) and blood tests that supported SjS diagnosis (normocytic normochromic anaemia, high erythrocyte sedimentation rate (ESR), lymphopenia, polyclonal hypergammaglobulinemia, complement levels in normal range, positive antinuclear antibodies (ANA) in a titer of 1/640 (fine speckled pattern), positive anti-SSA and anti-SSB, negative anti-dsDNA, anti-

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Sm, anti-cardiolipin, lupus anticoagulant, anti-RNP, anti-HCV and anti-HIV) despite negative salivary gland biopsy. In addition to educational measures aimed at controlling *Sicca* complaints and the use of artificial tears, we advise sun protection and prescribed hydroxychloroquine (HCQ) 400 mg daily (considering a body weight of 55 kg) with beneficial effects on skin lesions as no more episodes of purpura were reported. We verified the persistence of this benefit, even after the reduction to a maintenance dose of 200 mg daily. During the follow-up the patient irregularly adhered to medication, frequently stopping HCQ without medical advice. She referred that during interruptions of HCQ, she noticed some photosensitivity, fatigue and inflammatory arthralgias of hands but no noticeable joint swelling, and she admitted a significant improvement after reintroduction and maintenance of this drug.

No other clinical manifestations emerged during follow up, until 14 years after SjS diagnosis, in summertime, when she developed macular, erythematous, annular cutaneous lesions, some coalescing to form polycyclic plaques on the V-area of the neck, anterior chest, trunk and lower legs, about nine weeks after taking oral terbinafine, 250 mg per day, and topical econazole, prescribed for a suspected onychomycosis at Rheumatology follow up appointment. We examined the cutaneous lesions three weeks after their onset (Figures 1, 2 and 3) and noticed that the oldest ones had a hypopigmented central region and slightly scaly edges. She had consulted a Dermatologist the week before, who performed a skin biopsy, treated her with 30 mg of deflazacort per day and gave the indication to discontinue terbinafine. Since the onset of these skin lesions, the patient denied any other symptom, namely fever, mucosal ulcers, alopecia, myalgia, muscle weakness, inflammatory arthralgia, pleuritic pain and no other signs were found on clinical examination. Also, she denied having sunbathed and mentioned wearing more short and stained clothes. She confirmed that at the time of skin lesions onset she was not taking HCQ despite being prescribed. Complete blood count, ESR, C-reactive protein (CRP), complement levels, liver enzymes, kidney function and creatinine kinase were all in normal range. Urinalysis excluded proteinuria and active urinary sediment. In immunological evaluation, ANA had a titer of 1/320 (fine speckled pattern), anti-SSA and anti-SSB remained positive and anti-dsDNA (fluorescence enzyme immunoassay – FEIA), anti-Sm and anti-histones (immunoblot) were negative. Cutaneous biopsy identified "mild hyperkeratosis with parakeratosis and lichenoid inflammatory infiltrate sometimes with greater perifollicular expression, in a pattern that if properly supported by clinical changes may correspond to lupus". Macroscopic aspect of cutaneous lesions, along with the histological analysis of cutaneous biopsy and the absence of other symptoms, namely systemics, were in favour of lupus associated cutaneous lesions, most specifically SCLE. We reintroduced HCQ, 200 mg per day, and switched deflazacort for 30 mg of oral prednisolone (PDN) per day. Prompt improvement was observed, with a progressive disappearance of skin lesions which led to the implementation of progressive withdrawal of PDN, being below 10 mg per day after

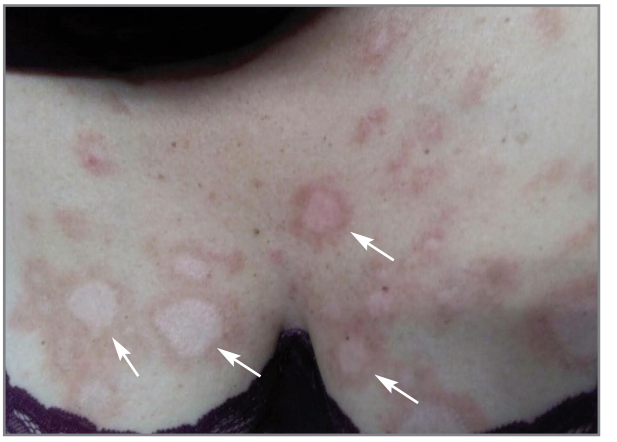

FIGURE 1. Annular, macular, erythematosus, cutaneous lesions with hypopigmented central region and slightly scaly edges on the V-area of the neck and anterior chest.

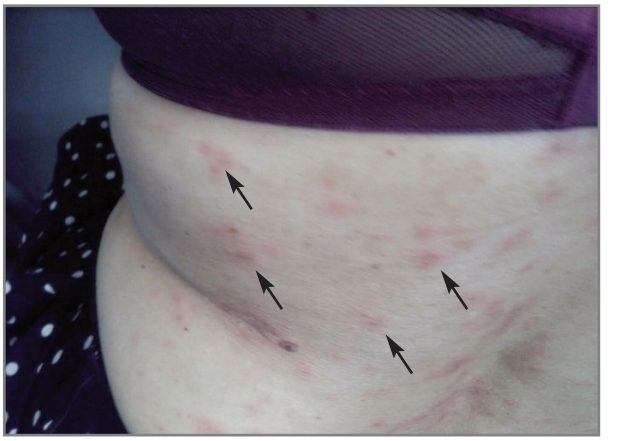

FIGURE 2. Macular, erythematosus, cutaneous lesions on the trunk.

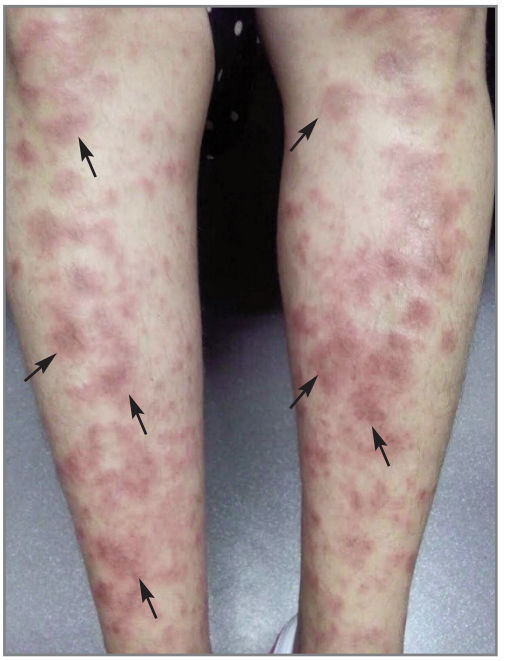

FIGURE 3. Macular, erythematous, annular cutaneous lesions, some coalescing to form polycyclic plaques on the lower legs.

1 month and completely withdrawn at the 5th month of treatment, without recurrence of symptoms, even after more than two years of follow up.

DISCUSSION

SCLE is divided in idiopathic or drug-induced forms. Drugs identified as capable of provoking DI-SCLE are commonly used ones, such as calcium channel blockers, angiotensin-converting enzyme inhibitors, thiazide diuretics, lansoprazole, pantoprazole, non-steroidal anti-inflammatory drugs but also the antifungal agent terbinafine, leflunomide and anti-TNF[1,2]. Clinical and serological characteristics of DI-SCLE are globally similar to those of idiopathic forms. In both cases, there is a slight predominance of females affected compared to males, cutaneous lesions are annular, polycyclic and/or papulosquamous, usually occurring in a characteristic sun-exposed distribution that includes the V-area of the neck, upper trunk and extensor aspects of the upper extremities, and SSA antibodies are almost universally present[1,2,6,7]. One clinical finding that could help to distinguish between DI-SCLE and idiopathic forms is the fact that it is possible to identify cutaneous lesions on lower legs in DI-SLE whereas they are rare below the waist in idiopathic forms[1,2,8]. Both in idiopathic and DI-SCLE but contrary to DI-SLE, systemic manifestations such as fever, arthritis, serositis or other visceral involvement are usually lacking and cytopenias are only rarely seen[1,9]. Prior autoimmunity had been reported in patients with SCLE, both in idiopathic and DI-SCLE[1,2,9,10]. In a published case series of 90 patients with SCLE, of which 12% had DI-SCLE, 28% had an associated auto-immune connective tissue disease (CTD), more frequently SjS, SLE, and rheumatoid arthritis[7]. Usually time between initiation of the drug and the onset of cutaneous lesions ranges from four to 20 weeks, depending on the drug itself, and cases occurring after years of treatment had also been reported[1,2]. Management of DI-SCLE, first of all, consists of discontinuing the responsible drug, which usually generates a significative improvement or resolution of cutaneous lesions within eight weeks[9]. Pharmacological treatment could be considered for severe and refractory cases, both in DI-SCLE or idiopathic forms. Systemic corticosteroids can be used transiently and may be associated with topical steroids and/or HCQ. Other immunosuppressive agents such as thalidomide, azathioprine, cyclophosphamide or mycophenolate can be considered for more resistant cases[1,9].

Terbinafine is a widely used broad spectrum oral antifungal agent frequently used to treat onychomycosis[11]. It is generally well tolerated and had a satisfactory safety profile[8]. Side effects occur in up to 10% of the patients, mainly transient gastrointestinal disorders[8]. Skin side effects have an estimated prevalence of about 2.5% and include urticaria, hyperpigmentation, as well as more serious disorders such as erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis, psoriasis flare, pustular psoriasis, erythroderma, bullous lupus erythematosus and SCLE[8,12]. SCLE cases attributed to terbinafine were published for the first time in 1998[13,14]. A systematic review of literature on DI-SCLE published in 2011 reported 29 cases of oral terbinafine induced SCLE[15] and we found three other published cases[9,11,16,17]. Also, one case of topical terbinafine induced SCLE in occupational context (foot masseuse) was reported[18]. Positive anti-SSA was present in at least 31 of these 33 patients (one patient had missing data and another one was anti-SSA negative but anti-SSB positive). A previous context potentially suggestive of autoimmunity was found in at least 24 patients, of which nine had a previous diagnosis of SLE, three of *Sicca* syndrome and one of SjS. The remaining nine patients had

seronegative arthritis, Raynaud phenomenon, photosensitivity, arthralgia, type 1 diabetes, autoimmune thrombocytopenic purpura, Kikuchi-Fujimoto disease and/or isolated positive ANA or "serologic evidence of autoimmune disease predisposing to photosensitivity". Cutaneous lesions appeared one to 12 weeks after starting terbinafine. Most of the patients (29, corresponding to 87,9%) needed targeted therapy (mostly topical or oral steroids, hydroxychloroquine, cyclosporine, dapsone) beyond the interruption of terbinafine and cutaneous lesions resolved in two to 15 weeks (table I)[6,8,19–24,9,11–14,16–18].

This clinical case raises the following question: is the occurrence of SCLE in this patient related with the previously known CTD, immunologically characterized by the presence of anti-SSA, or with the recent treatment with terbinafine?

It is known that anti-SSA antibodies are associated with the development of skin photosensitivity, and strong evidence of involvement of these antibodies in the development of epidermal change in SCLE, accentuated by ultraviolet light, have already been reported. The mechanisms by which anti-SSA induce keratinocyte damage are not yet exactly known, but it is thought that these involves the binding to SSA antigen and also the participation of mononuclear cells[5]. On the other hand, the pathomechanisms of terbinafine-induced SCLE had not yet been totally understood, but autoimmunity has been reported as a potential predisposing factor[17]. It has been suggested that terbinafine is capable of producing a photosensitivity state and due to its lipophilic and keratinophilic properties, it could have a direct toxic impact on epidermal keratinocytes, changing the configuration of nuclear antigens, inducing autoantibody formation[8]. In this clinical case, causality of terbinafine for the induction of SCLE is highly suggested by the close temporal association between the administration of the drug and the sudden onset of cutaneous lesions (nine weeks), timeline consistent with the window reported in previous published cases[2]. A second argument that points in favour of terbinafine causality is the involvement of lower legs, which are rarely involved in idiopathic SCLE[1,2,9]. The last argument is the rapid response of cutaneous lesions to discontinuation of terbinafine and the initiation of a targeted treatment.

Perhaps the most correct answer to our question is: terbinafine induced the occurrence of SCLE skin lesions, through its photosensitizing potential, enhancing the cytotoxic reaction dependent on anti-SSA and keratinocyte damage typical of SCLE[9]. In this case, the hypothesis of terbinafine-induced SLE was excluded since no other clinical manifestations beyond cutaneous lesions emerged and no suggestive analytical or serological changes of SLE were detected in blood and urine tests. Furthermore, anti-histones antibodies, present in up to 95% of DI-SLE and considered as the serological markers of DI-SLE (although described in up to one-third of DI-SCLE)[1,15], were negative.

Because of the severity of cutaneous lesions after stopping terbinafine, we decided to give oral PDN and re-introduced HCQ that was previously stopped by the patient without our consent. She had a good response to therapy and to date, more than two years after the onset of the condition, no recurrence had been seen.

This case highlights the importance of avoiding the prescription of terbinafine to patients with CTD, especially for patients with photosensitivity, SjS and/or with positive anti-SSA. Awareness among Rheumatologist about drugs implicated in DI-SCLE is necessary, name-

TABLE I. SUMMARY OF THE MAIN ASPECTS ON TERBINAFINE AND CUTANEOUS LUPUS AVAILABLE IN LITERATURE

Time to onset of symptoms after terbinafine introduction	1 – 12 weeks[19,22]
Skin involvement	Sun-exposed distribution (V-area of the neck, upper trunk, extensor aspects of the upper extremities, lower legs)[8,15,19]
Comorbidities	Background of previous autoimmunity often present[7]
Laboratory findings	Anti-SSA almost always present[1,2,6,7]
Treatment	Stopping terbinafine. Corticosteroids (oral and/or topical) and hydroxychloroquine can be added. Consider azathioprine, cyclosporine or dapsone for more resistant cases[4,7,19]
Time to resolution of skin lesions	2 to 24 weeks[6,8]

ly because they are commonly used. For terbinafine, in particular, it will be more appropriate to confirm the diagnosis of onychomycosis by microscopy and/or culture before initiating the treatment, in order to avoid unnecessary iatrogenesis. If the decision to prescribe terbinafine is made, it is important to inform the patient that adverse skin effects may occur, to recommend discontinuing the treatment immediately at the onset of cutaneous lesions and to seek medical advice. This case also highlights the importance of the recommendation for photoprotection in all anti-SSA positive patients[25].

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