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Drug-induced anti-Ro positive subacute cutaneous lupus in a man treated with olmesartan

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Abstract

A 66-year-old man presented to the outpatient dermatology clinic with a chief complaint of a pruritic rash on his upper trunk and proximal upper extremities, which had been present for three weeks. Upon examination, he was found to have an erythematous, annular, and polycyclic eruption on the chest, upper back, and proximal extremities. A clinical diagnosis of subacute cutaneous lupus erythematosus (SCLE) was made. The patient was found to have a positive anti-nuclear antibody (ANA) in a speckled pattern and a positive anti-Ro antibody. A biopsy revealed an interface and lichenoid dermatitis with dermal mucin deposition, consistent with subacute cutaneous lupus erythematosus. The patient reported that he had recently been diagnosed with hypertension and began treatment with olmesartan, a potassium-sparing diuretic that blocks the angiotensin II receptor, commonly used as an antihypertensive or in patients with heart failure. Cutaneous reactions to olmesartan are rare and reported in <1% of patients in post-marketing surveillance. The patient discontinued use of olmesartan and the rash completely resolved within three weeks. To date, there are no other reported cases of drug induced SCLE in patients taking olmesartan to our knowledge.

Keywords: drug-induced subacute cutaneous lupus, olmesartan, anti-Ro/SSA

Introduction

Drug induced subacute cutaneous lupus erythematosus (DI-SCLE) is a relatively uncommon phenomenon characterized by photo-distributed

polycyclic or papulosquamous plaques [1]. Pathogenesis is possibly related to keratinocyte apoptosis, release of inflammatory mediators, and subsequent immune sensitization [1, 2]. Although DI-SCLE has been reported previously with antihypertensive agents such as calcium channel blockers, hydrochlorothiazide, and angiotensin-converting enzyme inhibitors there are no reported cases in the literature of DI-SCLE to olmesartan, an angiotensin II receptor antagonist. Our case brings attention to the development of DI-SCLE related to olmesartan, and the importance of reviewing a patient's medication list when considering the diagnosis of subacute cutaneous lupus erythematosus.

Case Synopsis

We present a 66-year-old man, with past medical history of hypertension, who presented to our dermatology clinic with a chief complaint of a pruritic rash on his upper trunk and proximal upper extremities, present for three weeks. The patient stated that he began taking olmesartan for treatment of his hypertension 8 weeks prior to the onset of the rash. On physical exam, polycyclic and annular erythematous, scaly plaques covering the upper back were noted (**Figure 1**). A punch biopsy for hematoxylin and eosin (H&E) was obtained. The biopsy revealed interface and lichenoid dermatitis (**Figure 2A**) with necrotic keratinocytes and dermal mucin deposition (**Figure 2B**). Pertinent labs revealed antinuclear antibodies (ANA) positivity in a speckled pattern, as well as anti-Ro/anti-Sjogren's-syndrome-related antigen A (SSA) antibody



Figure 1. Polycyclic and annular erythematous, scaly plaques covering upper back.

positivity. These findings, coupled with the recent addition of olmesartan, supported the diagnosis of

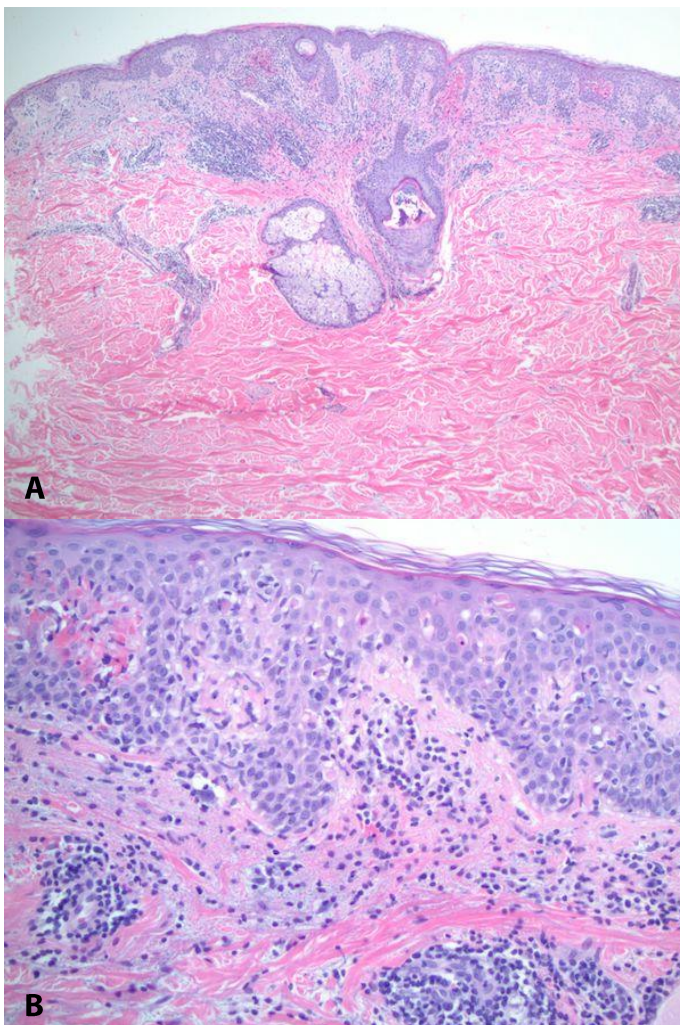


Figure 2. A) Punch biopsy demonstrating interface and lichenoid dermatitis. H&E, 100 \times . **B)** Necrotic keratinocytes and dermal mucin deposition. H&E, 200 \times .

DI-SCLE. Olmesartan was discontinued, and the patient was prescribed a high potency topical steroid. At follow up, three weeks later, the eruption had completely resolved.

Case Discussion

The first case of DI-SCLE was reported by Reed et al. in 1985, associated with hydrochlorothiazide [3]. Since that time, more than 50 drugs have been implicated in cases of DI-SCLE. However, the most commonly associated drugs are thiazide diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors, proton pump inhibitors, statins, anti-fungals, anti-epileptics, and chemotherapy agents [4]. It was previously estimated that 6-20% of cases of SCLE were drug induced. However, recent research suggests the incidence of DI-SCLE may account for 71% of all cases of SCLE [5].

The mechanism of DI-SCLE is postulated to be a multifactorial process that includes induction of anti-Ro/SSA antibody production, increased expression of a nti-Ro/SSA, or enhanced phototoxicity. It has been hypothesized that drugs may enhance Ro/SSA antigen expression or increase antibody production. However, this is being called into question as it is difficult to envision one mechanism in which many different drug classes could induce the same disease process [2]. One theory is a process called "photopharmacological isomorphic response" in which many drugs induce a photosensitive state that nonspecifically induces SCLE skin lesions in individuals who are genetically predisposed to developing SCLE via an isomorphic response [2]. This hypothesis is supported by the finding that many patients with systemic lupus erythematosus demonstrate antibody positivity many years prior to developing clinical illness [2, 6].

Drug induced subacute cutaneous lupus erythematosus and idiopathic SCLE can be difficult to distinguish clinically and paraclinically. Both entities present with photo-distributed polycyclic or papulosquamous plaques on the trunk or upper extremities. However, patients with DI-SCLE may present with more widespread and inflammatory lesions and are more likely to have cutaneous involvement of the lower legs [4, 7]. Patients with DI-

SCLE experience bullous, targetoid, and vasculitic manifestations more often than patients with idiopathic SCLE. However, patients with idiopathic SCLE may be more likely to experience systemic features including arthralgias, xerophthalmia, and nephropathy [7]. Age at disease onset is often higher for patients with DI-SCLE with a reported mean age of 59, potentially related to increasing number of medications with age [7-9].

Drug induced subacute cutaneous lupus erythematosus and idiopathic SCLE are difficult to distinguish histopathologically as both can demonstrate focal vacuolization of the epidermal basal layer associated with perivascular dermal lymphocytic infiltrate [2]. Immunologically both entities have been shown to present with granular deposition of IgM, IgG, and C3 in a band at the epidermal-dermal junction [2]. However, a recent multicenter study demonstrated that mucin deposition and direct immunofluorescence positivity for granular IgM and C3 deposits on the basement membrane zone may be significant for SCLE, whereas leukocytoclastic vasculitis suggests a diagnosis of DI-SCLE [9].

With regard to serology, SSA autoantibody rates are not significantly different between DI-SCLE and SCLE, with positivity in approximately 74% of both patient groups [4]. These findings, along with variable incubation and resolution periods for DI-SCLE, can make distinguishing between SCLE and DI-SCLE challenging. The mean time from drug initiation to onset of rash is 28 weeks and mean time from drug discontinuation to resolution of DI-SCLE is 7 weeks [2, 4]. However, much variation has been reported both between drug classes and individual cases [2, 4]. Several cases have also been reported of patients who experienced multiple occurrences of DI-SCLE induced by more than one pharmacologic group [4]. Although recognition and discontinuation of the implicated medication is the cornerstone of DI-SCLE treatment, other common treatment modalities include topical corticosteroids, oral prednisone, hydroxychloroquine, and topical tacrolimus [2]. Physicians should always review a

patient's medication list when considering the diagnosis of SCLE as up to 71% of all cases may be drug induced [5].

Our patient first developed signs of SCLE 8 weeks after initiating anti-hypertensive therapy with olmesartan. On physical exam, polycyclic and annular erythematous, scaly plaques covering the upper back and bilateral upper extremities were noted. Laboratory work revealed positivity for both the ANA and anti-Ro/SSA antibody. A biopsy for direct immunofluorescence was not performed in our patient. However, H&E staining revealed interface and lichenoid dermatitis. Three weeks after discontinuing olmesartan and using potent topical corticosteroids, the rash had completely resolved. There are no previous reports in the literature of DI-SCLE related to olmesartan. Furthermore, cutaneous reactions to olmesartan are reported in <1% of patients in post-marketing surveillance [10]. There have been 955 reported "skin and subcutaneous tissue disorders" related to the use of olmesartan since 2002 in the FDA Adverse Event Reporting System [11]. Although none of these cases were defined as DI-SCLE, the possibility of under reporting cannot be excluded. Many of these adverse events were reported under generalized terms such as "drug reaction," "dermatitis," and "rash" and reported cases are not verified [11].

The time from drug initiation to onset of rash, as well as time from drug discontinuation to resolution of DI-SCLE were well below reported averages in our patient. Although it is known that there is variation between drug class, there is no current literature regarding symptom onset following initiation of drug for angiotensin II receptor antagonist. The possibility that olmesartan could trigger SCLE skin lesions via an isomorphic response is probable as there are documented cases of photosensitivity resulting from olmesartan as well as other drugs in the angiotensin II receptor antagonist class [11, 12]. To date our patient has not had recurrence of DI-SCLE and has not shown signs of underlying autoimmune disease that could account for ANA or anti-Ro/SSA antibody positivity.

Conclusion

In conclusion, a comprehensive review of medications should be performed for patients in which the diagnosis of SCLE is being considered. Failing to recognize SCLE as a drug induced phenomenon, when appropriate, may result in intensive pharmacological treatment placing the

patient at risk for experiencing unnecessary side effects or incurring unnecessary medical expenses.

Potential conflicts of interest

The authors declare no conflicts of interest.

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