Amlodipine-Induced Subacute Cutaneous Lupus Erythematosus Localized to Non-Sun-Exposed Areas

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Abstract
The cutaneous manifestations of subacute cutaneous lupus erythematosus (SCLE), a subset of cutaneous lupus erythematosus, arise most often in sun-exposed areas. We report a case of SCLE with atypical distribution, following treatment with amlodipine. This highlighted a possible clue that can be used to clinically distinguish a drug-induced case from an idiopathic disorder. A 92-year-old Japanese woman presented with a 2-month history of progressive erythematous, papulosquamous rash, and annular plaques in non-sun-exposed sites with no systemic symptoms. Irbesartan/amlodipine besilate combination tablets were prescribed 8 months earlier for hypertension. The appearance of the skin eruptions, results of immunopathological findings, and temporal relationship between the rash and drugs were suggestive of a diagnosis of drug-induced SCLE, which was confirmed by the spontaneous resolution of these cutaneous eruptions within 4 weeks after cessation of amlodipine treatment. The evaluation of possible associations with medications should be performed in patients presenting with clinical features characterizing SCLE in atypical sites (non-sun-exposed areas).
Introduction

Subacute cutaneous lupus erythematosus (SCLE) is a subset of cutaneous lupus erythematosus and typically presents as psoriasiform or annular erythematous plaques in sun-exposed areas with minimal or nonexistent systemic findings [1]. SCLE may occur in association with systemic lupus erythematosus, as an idiopathic eruption, or as a drug-induced disorder. The latter two subtypes may be indistinguishable in the absence of distinct medication history, while certain features may be more likely to occur in each subtype [2]. Herein, we describe a case of SCLE localized to non-sun-exposed sites, following treatment with amlodipine.

Case Report

A 92-year-old Japanese woman presented with a 2-month history of progressive pruritic eruptions on her lower body. Her medical history included hypertension and hyperlipidemia, for which irbesartan/amlodipine besilate combination tablets and rosuvastatin calcium were prescribed 8 months earlier. Before presenting to our department, antihistamines and topical 0.1% hydrocortisone butyrate ointment (twice daily for 2 weeks) were prescribed, which provided no significant clinical improvement. She was otherwise well with no systemic symptoms. She had no history of photosensitivity or allergies. Physical examination showed erythematous, papulosquamous eruptions, and annular plaques with slight scales, which partially coalesced to form polycyclic patchy patterns on the buttocks and lower limbs (Fig. 1a, b). Complete blood count and liver and renal function tests were unremarkable. Serological analyses for antinuclear antibody, anti-double stranded DNA, anti-Sjögren’s-syndrome-related antigen A (anti-Ro/SS-A), and anti-Sjögren’s-syndrome-related antigen B antibodies were negative. The potassium hydroxide (KOH) preparation test showed negative results. Histopathological examination of a skin lesion at the center of the left buttock revealed slight hydropic degeneration.

Fig. 1. Pink to red papules, plaques, and annular erythematous plaques with focal polycyclic patterns in non-sun-exposed areas. (A, buttocks; B, lower limbs).
of the epidermal basal layer with lymphocyte infiltrates beneath the epidermis. There were sparse lymphocytic perivascular infiltrates with few eosinophils in the upper dermis (Fig. 2). Direct immunofluorescence was negative. Marked increase in dermal mucin or morphological evidence of fungal hyphae was not observed. Considering the appearance of the skin eruptions, absence of organ-threatening complications, and histopathologic findings, SCLE-like changes were suspected. Additionally, due to absence of clinical signs of systemic lupus erythematosus and temporal relationship between these cutaneous eruptions and medications, a provisional diagnosis of drug-induced SCLE (DI-SCLE) was considered. The prescribed drugs were sequentially discontinued, starting with those known to be frequently associated with drug reactions. Initially, amlodipine was discontinued and irbesartan was administered in combination with rosuvastatin calcium. Within 4 weeks following cessation of amlodipine treatment, the cutaneous eruptions resolved spontaneously, and this supported establishing a diagnosis of DI-SCLE.

**Discussion/Conclusion**

Several classes of drugs have been proposed as triggers for SCLE, including antihypertensives, lipid-lowering agents, proton pump inhibitors, and antifungals [3]. Although the number of SCLE cases related to antihypertensive use has reportedly been decreased in recent years, antihypertensives are widely recognized in the literature as the class of drugs that are most frequently associated with DI-SCLE. Moreover, publication bias in selecting associations with rare or novel drugs should be considered when assessing changes in the incidence of DI-SCLE reports according to drug category [4, 5]. Diuretics are the most represented class followed by cardiovascular drugs. Amlodipine, a calcium channel blocker, is the most common cardiovascular drug that induces SCLE [6]. The incubation and resolution periods for DI-SCLE may vary for different drug classes. The latency period ranges from 3 days to 11 years (median latency, 6 weeks) with longer periods for calcium channel blockers. The mean and median resolution periods after withdrawal of triggering drugs were 7.3 (range, 1–32 weeks) and 4 weeks, respectively [7].

DI-SCLE typically presents with erythematous, annular polycyclic, or papulosquamous lesions [8]. Anti-Ro/SS-A antibodies are serological markers of DI-SCLE and are observed in 70% of cases. Few patients with DI-SCLE are reported to be positive for anti-Sjögren’s syndrome-related antigen B and anti-histone antibodies [6]. Although most patients with DI-SCLE are anti-Ro/SS-A-positive, presence of the antibodies is not pathognomonic. Histopathologically, DI-SCLE presents as an interface dermatitis with focal vacuolization of the basal layer of the epidermis and perivascular dermal lymphocytic infiltrate [7]. Direct immunofluorescence has been found to be positive in approximately 20% of cases of DI-SCLE [6].
The clinical, serological, and histological features of DI-SCLE are similar to those of idiopathic SCLE (I-SCLE) [8]. Although no standard diagnostic criteria have been developed, the diagnosis of DI-SCLE can be established in patients with clinical features of I-SCLE and significant medication history, in whom cutaneous lesions improve after the withdrawal of suspected drugs. Additionally, considering the limitations of causality evaluation, the identification of characteristic features of DI-SCLE infrequently found in patients with I-SCLE may increase the strength of the association [2].

In our patient, the clinical appearance was comparable to the clinical features of DI-SCLE. Although the location of her skin symptoms was not typical for SCLE, a recent study reported that compared to patients with I-SCLE, patients with DI-SCLE showed widespread lesions in both sun-exposed (trunk, upper extremities) and non-sun-exposed (legs) areas [2]. Moreover, a retrospective study of 165 patients with I-SCLE and 67 patients with DI-SCLE found that in the overall cohort, skin lesions were distributed in sun-exposed areas in 101 patients (50%), and on individual assessment of the two groups, cutaneous involvement in sun-exposed areas was less frequent (55% vs. 36%) in patients with DI-SCLE [6]. These reports, together with our findings, suggest that the distribution of the skin rash in non-sun-exposed areas, such as the lower extremities, is a clinical clue to identify drug-induced cases. The histological features in our case were not entirely specific; however, the findings of perivascular lymphocytic infiltrates more confined to the upper dermis with eosinophils along with slight interface changes were suggestive of a possible drug-induced nature of the SCLE-like rash. Considering the prolonged course of the rash, our skin biopsy specimen may represent late-phase classic DI-SCLE lesions, which show nonspecific alterations, namely inflammatory infiltrates of mononuclear cells in the upper dermis with unremarkable epidermal changes [2]. Additionally, less frequent immunopathological findings of DI-SCLE include mucin deposition and positive immunofluorescence [6]. Generally, skin lesions exposed to sunlight can be used for diagnosing lupus erythematosus to avoid the problem of false-negative results due to decreased sensitivity in non-sun-exposed areas [9]. A previous study has reported positive direct immunofluorescence in 8 of 11 DI-SCLE cases (73%), wherein biopsy specimens were obtained from sun-exposed cutaneous lesions [2]. Therefore, in our case, the site of skin biopsy (non-sun-exposed area) might be the most likely explanation of the negative direct immunofluorescence result. Moreover, although lichen planus is a key differential diagnosis of all variants of lupus erythematosus, the histological findings of epidermal parakeratosis and lichenoid interface inflammatory reaction, which would indicate drug-induced lichen planus, were not found in our patient [10].

Based on clinical manifestations, the differential diagnosis of SCLE includes multiple other cutaneous disorders that may present with annular, erythematous skin lesions. In general, careful assessment of annular features and their clinical and pathologic aspects can be helpful for narrowing the differential diagnosis. In some diseases, such as erythema annulare centrifugum (EAC) and tinea corporis, erythematous annular lesions represent the most common clinical presentation. However, annular lesions are not a common feature of other differential diagnoses including psoriasis, sarcoidosis, or mycosis fungoides, possibly demonstrating annular lesions only as occasional or incidental features. In our case, the patient showed erythematous annular plaques with slight scale without systemic signs or symptoms. Considering the epidemiological setting, a combination of careful evaluation of cutaneous lesions and the KOH preparation test would be useful for identifying EAC or tinea corporis, the most common disorders in the list of differential diagnosis. EAC is an inflammatory reactive disorder presenting with arcuate or annular, erythematous patches or plaques with a rim of fine scale presenting more centrally (“the trailing scale”). A skin biopsy is useful when the diagnosis of EAC is not clear after clinical assessments. The histopathologic findings of EAC include dense, perivascular, and lymphocytic inflammatory infiltrate limited to the superficial vascular plexus [11]. In contrast to EAC, a scale in tinea corporis, a dermatophyte infection, is typically found throughout the leading edge of annular
plaques ("the leading scale") rather than the trailing edge ("the trailing scale"). The KOH preparation test can rapidly establish a diagnosis of tinea corporis [12]. Moreover, findings inconsistent with those of EAC or tinea corporis, such as a history of blistering, erosions, or mucosal involvement, could raise suspicion of alternative diagnoses. In our case, erythematous annular plaques resembling those of EAC and tinea corporis were observed. However, the KOH preparation test showed negative results. Moreover, the scale did not have characteristics of EAC or tinea capitis. Further, the histopathological examination did not reveal any characteristic features of EAC and other differential diagnoses. Therefore, we ruled out these disorders.

In conclusion, our report highlights the importance of an integrated clinical and immunopathological approach to differentiate DI-SCLE from I-SCLE. It also demonstrates the clinical usefulness of a methodological approach of sequential drug withdrawal in diagnosis of DI-SCLE. Furthermore, since only a few studies have evaluated the sites of DI-SCLE, this report suggests the need for assessing atypical sites (non-sun-exposed areas) in cases with clinical features similar to those of DI-SCLE.

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Statement of Ethics

The authors obtained the patient’s written informed consent for the publication of this case report and any accompanying images. Ethical approval is not required for this study in accordance with local or national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Takahiro Mizuta reviewed the patient’s case notes and relevant literature and wrote the clinical case. Miyuki Kato was responsible for identifying and managing the case, as well as for reading and suggesting improvements to several drafts. Both authors have read and approved the content of the final report.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.
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