Toxic epidermal necrolysis-like lupus erythematosus: A case report

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ABSTRACT:

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Toxic epidermal necrolysis-like lupus erythematosus, a rare variant of cutaneous lupus erythematosus is characterized by sheet-like desquamation of the skin predominating on photo-distributed area. Clinically, the lesions can present similar to classical toxic epidermal necrolysis. This condition is complicated to be diagnosed due to the rarity of the disease and less information.

We report a case of 32-year-old Thai woman who has had a long-standing history of systemic lupus erythematosus. The patient presented with a 2-month history of developing widespread, targetoid, red to violaceous photosensitive rash, which then progressed to sheet-like desquamation predominating on sun-exposed area. Histopathology and direct immunofluorescence are compatible with lupus erythematosus. The patient was diagnosed as TEN-like LE. She was prescribed high dosage of intravenous corticosteroid and other immunosuppressive drugs, together with hydroxychloroquine. She responded well to the treatment within a few days.

Key words: Toxic epidermal necrolysis, lupus erythematosus, epidermal necrolysis

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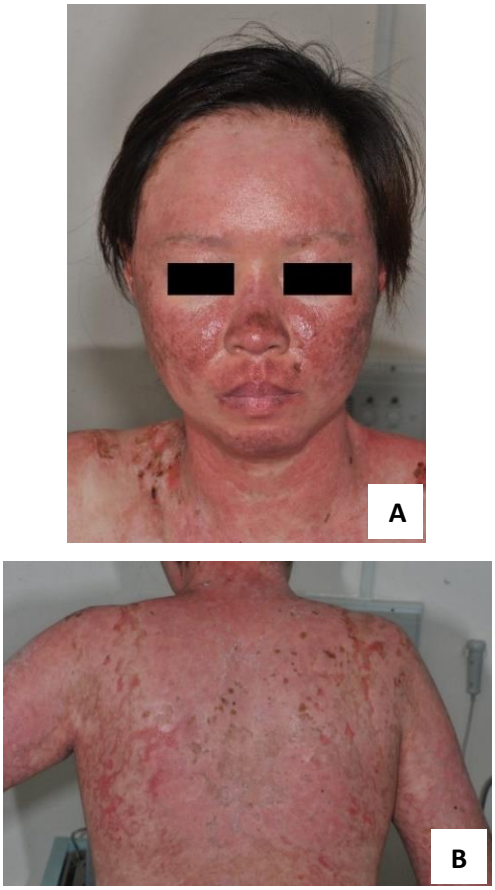

Figure 1A, 1B Generalized sheet-like desquamation on the face, V-neck, trunk and extremities, noted on photo-distribution area

Introduction

Toxic epidermal necrolysis (TEN) is an acute life-threatening reaction, first reported by Lyell[1], largely caused by drug hypersensitivity.[2] The reaction has also been described in terms of acute graft-versus-host disease (GVHD)[3], *Mycoplasma pneumoniae* infection[4], vaccinations,[5] and systemic lupus erythematosus (SLE)[6].

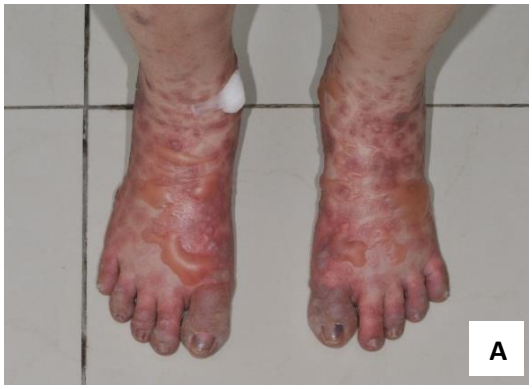

Figure 2A Localized erythematous targetoid rash and tense bullae on dorsal side of both feet

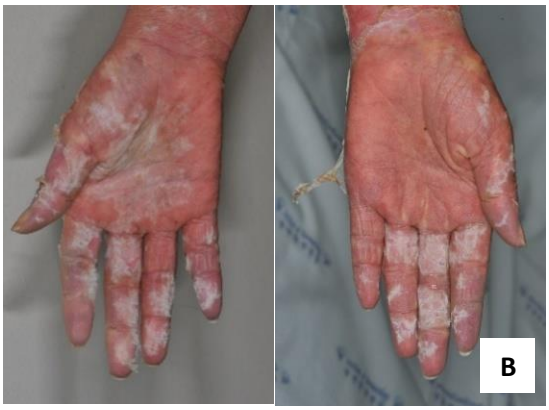

Figure 2B Localized bilateral desquamation of the skin on both palms

Clinically, TEN in systemic lupus erythematosus (SLE) patients has been challenging in terms of diagnosis. SLE patients have to take multiple medications, and the effects of these medications can produce lesions that may resemble vesiculobullous lesions. In addition, little information on TEN is provided by existing literature[6-9]. This report discusses a patient who developed clinical symptoms of an

active SLE rash that mimicked those of classical TEN.

Case report

A 32-year-old Thai woman with a 12-year history of SLE presented with a 2-month history of widespread, painful, targetoid, red to violaceous, photosensitive rash on her face, chest, trunk, and all extremities without fever. This patient went to a public hospital and was diagnosed with active cutaneous lupus erythematous. The patient was prescribed 500 mg of intravenous cyclophosphamide every 2 weeks, 20 mg of prednisolone per day, and 150 mg of oral cyclophosphamide per week to control the rash.

Two weeks later, the patient was exposed to sunlight during a trip to Khao-Yai. The following week, the eruption progressed to a generalized erythematous rash. The patient was then admitted to a private hospital. The diagnosis was toxic epidermal necrolysis (TEN) suspected to be a result of taking hydroxychloroquine. Although the patient reported taking hydroxychloroquine approximately 10 years ago, the drug had since been discontinued. Initially, 8 mg of dexamethasone was intravenously injected every 4 hours for 4 days, and 40 mg of prednisolone and 25 mg of cyclosporine were given daily. However, the patient's symptoms were not alleviated, so she was referred to our institute.

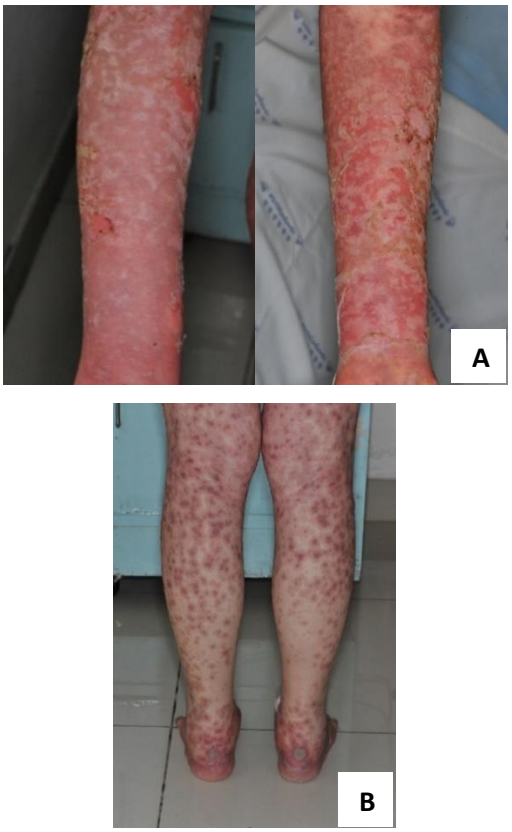

Figure 3 Bilateral erythematous targetoid rash on both upper (A) and lower extremities (B)

A physical examination revealed generalized tense bullae with target-like lesions. Some lesions had progressed to erosive patches with sheet-like desquamation on the face, V-neck area, trunk, and all extremities, including palms and soles. The rash covered more than 30% of the body's surface area, as seen in Figures 1, 2, 3, and 4. A few erosions had formed on the hard

palate and lips. The patient's eyes and genitalia had no remarkable characteristics

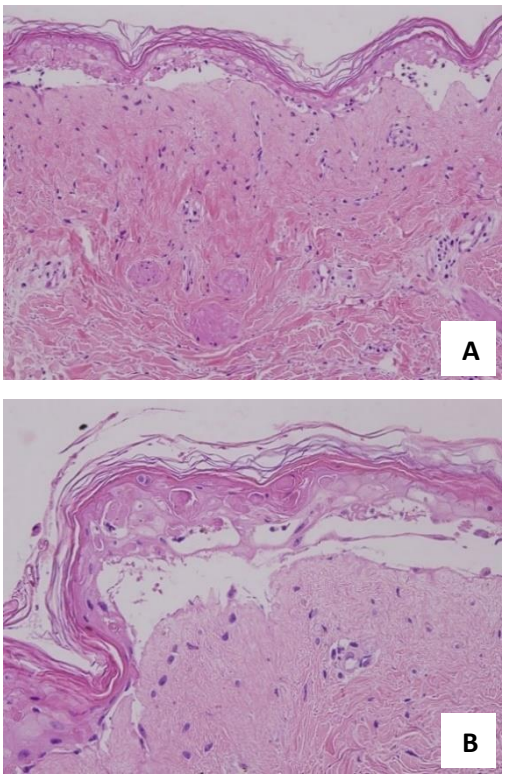

Figure 4 Histopathologic study on day 7 from the onset of skin eruption revealed subepidermal separation, massive epidermal necrosis with sparse perivascular infiltration by lymphocytes. (H&E; original magnification: **A.** x200, **B.** x400)

She had an underlying disease, namely systemic lupus erythematosus, which had been diagnosed in 2006. The patient had gone for regular follow-ups with a rheumatologist since diagnosis. The criteria for diagnosis included malar rash, discoid lupus erythematosus, oral ulcer, lymphopenia, antinuclear antibody (ANA) positive 1:1280 in speckle pattern, and positive anti-double strand DNA. The disease was well controlled. The patient's medication, when the disease flared, was prednisolone (20 mg daily), hydroxychloroquine (600 mg per weekly), azathioprine (100 mg per day), cyclosporine (125 mg per day), and methotrexate (12.5 mg per week). The disease had flared up approximately 3 months prior to admission as an active rash and lymphopenia. The patient had a history of dapsone and ciprofloxacin allergies and had developed a generalized pruritic maculopapular rash upon taking these drugs.

The histopathology from the left arm at day 7 after the onset of the rash was reviewed. It showed subepidermal separation, massive epidermal necrosis, and basal cell vacuolization with sparse superficial perivascular infiltration with lymphocytes, as seen in Figure 4. Direct immunofluorescence studies demonstrated positive IgG, IgM, and C3 deposition in linear granular pattern on the basement membrane zone. A skin biopsy was repeated on the targetoid lesion on the left leg. A histopathology showed subepidermal separation with necrotic keratocytes on the basal cell layer. Vacuolar degeneration of the basal cell layer was seen, and the epidermis showed hyperkeratosis. There were both superficial and deep perivascular lymphoplasmacytic infiltration with periadnexal inflammation. Direct immunofluorescence was

negative. We hypothesized that the negative DIF was a result of the healed lesion. Other investigation revealed lymphopenia (430/mm^3; normal >1,500/mm^3) with normal hematocrit and platelet count. The ANA titer was positive at titer 1:2560 (speckle pattern). The anti-Ro (SS-A) and anti-La (SS-B) were both positive, but the anti-dsDNA and rheumatoid factor were negative. The U1RNA antibody was positive. C3 level was normal at 98 mg/dl (normal 90-180 mg/dl). The highly C-reactive protein (hs-CRP) was mildly elevated at 3.3 mg/L (normal 0-3 mg/L), and the erythrocyte sedimentation rate was also mildly elevated at 29 mm/h (normal <20 mm/h). The liver function test and urinalysis were unremarkable. A herpes simplex virus antibody, varicella zoster antibody, and *M. pneumoniae* antibody tests were negative.

Table 1 The classification system adapted from existing literature[10, 11]

LE-specific vesiculobullous skin disease
1) TEN-like ACLE
2) TEN-like SCLE
3) TEN occurring in SLE patients without conventional LE-specific skin lesions
4) Vesiculobullous annular SCLE
5) Vesiculobullous chronic cutaneous LE
LE-nonspecific vesiculobullous skin disease
Autoimmune
1) Dermatitis herpetiformis (DH)-like vesiculobullous LE
2) Epidermolysis bullosa aquisita (EBA)-like vesiculobullous LE
3) Bullous pemphigoid (BP)-like vesiculobullous LE

The clinical presentation and lab investigations in our patient were compatible with TEN-like ACLE. The patient was prescribed a high dosage of corticosteroid 1 mg/Kg/day in combination with intravenous cyclophosphamide. Oral cyclosporine 25 mg and hydroxychloroquine 200 mg/day were re-administrated. The desquamated skin improved within 2-3 days. The patient was discharged following 10 days of stay.

Discussion

Vesiculobullous eruption in SLE patients is uncommon. Practitioners must distinguish SLE-related from non SLE-related conditions, particularly cutaneous drug eruption or other

vesiculobullous diseases. Sontheimer categorized SLE-related vesiculobullous lesions into LE-specific and LE-nonspecific forms[10], as shown in Table 1.

Table 2 Diagnostic features of classical TEN, TEN-like LE, and bullous LE[6, 9, 11, 12]

	Toxic epidermal necrolysis	**TEN-like LE (ACLE/SCLE)**	**Bullous LE**
Clinical	Full-thickness, sheet-like, vesiculobullous change		Tense bullae
Distribution	Widespread, rapid progression (days)	Photo-distribution, gradual progression (weeks to months)	Photo-distribution
Mucous membrane involvement	Severe	Less severe or not involvement	Present in 1/3 of patients
Systemic involvement	Systemic toxicity (e.g. pulmonary, liver)	Organ specific of LE (e.g. lupus nephritis, hematologic involvement)	Organ specific of LE (e.g. lupus nephritis, hematologic involvement)
Serology	Negative	ANA positive, anti-Ro/La positive	ANA positive
Histopathology	Full thickness epidermal necrosis with sparse superficial lymphocyte inflammatory cell infiltration	Full thickness epidermal necrosis with sparse superficial lymphocyte inflammatory cell infiltration Features of interface dermatitis	Subepidermal separation with superficial dermal neutrophilic infiltration
DIF	Negative	Possibly positive for LE	Positive

LE-specific vesicullobullous lesions are classified as extensive interface dermatitis that can occur in acute, subacute, or chronic cutaneous lesions. The clinical vesiculobullous eruption and sheet-like desquamation of the skin are the result of massive vacuolar degeneration of the epidermal basal cell layer. Mandelcorn and Shear suggested that subacute progression may reflect a gradual apoptosis of basal keratinocytes, which differs from rapid injury in classical TEN.[6] Additionally, most TEN-like ACLE/SCLE patients have other systemic organ involvement, such as lupus nephritis, hematologic involvement.[11] Histological findings

may resemble TEN and some features of LE, composed of full-thickness epidermal necrosis, basal vacuolization, and necrotic keratinocyte, particularly in dermo-epithelial junctions. Direct immunofluorescence demonstrates variable results from negative or positive as in lupus. The patient came to our institute with vesiculobullous lesions and later progressed to sheet-like desquamation of the skin. The clinical presentation and histopathology were compatible with TEN-like ACLE.

Other vesiculobullous eruptions that may occur in LE patients include bullous LE and associated immunobullous disorders. Bullous LE is a chronic, widespread, non-scarring bullous eruption occurring in patients with active SLE. Other immunobullous disorders that may occur in association with LE include bullous pemphigoid, epidermolysis bullosa acquista, and dermatitis herpetiformis. Each of these diseases has a set of distinctive autoantibody-associated vesiculobullous clinical-pathologic entities, which can occur as isolated autoimmune skin diseases in association with SLE. In these LE-nonspecific vesiculobullous diseases, the histopathological evaluation does not have interface dermatitis characteristic of LE-specific skin disease.[11] The differential diagnoses include TEN, TEN-like LE, and bullous LE and are summarized in Table 2.

Much research has proposed that SLE is one of the risk factors in developing SJS/TEN.[12, 13] The patient was allergic to dapsone and ciprofloxacin, but she had not taken these medications. Her medication history included hydroxychloroquine[14], methotrexate[15], azathioprine[16], and cyclophosphamide[17], all of which had been initially been suspected to be the cause of TEN. The duration of drug exposure to skin reactions usually ranges from 4 to 30 days.[18] However, this patient had already received these drugs for many years before the onset of the rash.

Currently, treatment of TEN-like ACLE is controversial. The aim of treatment is to control SLE symptoms. Many researchers have suggested a high dosage of corticosteroid, such as pulse intravenous methylprednisolone 80 mg/day[9,11,19] or pulse intravenous dexamethasone 18 mg/day[7]. IVIG[6, 11] and plasmapheresis[20] have also proven to be beneficial in acute phases. A combination of systemic corticosteroid with immunosuppressive agents (e.g. cyclophosphamide, cyclosporine, azathioprine, etc.) is required to control disease symptoms during long-term follow up.

Conclusion

This report has discussed a SLE patient with severe vesiculobullous eruptions defined as TEN-like ACLE. The symptoms resembled classical TEN but had a number of unusual features, such

as photo-distribution, the gradual onset of the rash, and positive serology. Clinicians should consider TEN-like ACLE in cases of mixed dermatological findings.

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