

Toxic epidermal necrolysis-like acute cutaneous lupus erythematosus (TEN-like ACLE) in SLE patients: a report of two cases

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Summary

Background: Acute cutaneous lupus erythematosus (ACLE) is a specific lesion in systemic lupus erythematosus (SLE) patients. ACLE can be categorized into localized ACLE, generalized ACLE and toxic epidermal necrolysis-like ACLE.

Toxic epidermal necrolysis (TEN) that occurs in SLE patients has been infrequently reviewed. This condition is complicated to diagnose because medication can produce a blistering eruption that resembles vesiculobullous disease in SLE.

Objective: To describe two cases of newly diagnosed SLE that had a cutaneous presentation compatible with TEN-like ACLE.

Case reports: Characteristics of two patients presenting with TEN-like ACLE and SLE are presented.

Conclusion: The authors have described two cases of TEN-like ACLE which occurred in the context of systemic involvement of SLE. The cutaneous lesion was gradually progressed, with less mucosal involvement and mainly photodistributed. The authors suggest that the complexity and rarity of this condition could be related to systemic severity of SLE. (*Asian Pac J Allergy Immunol* 2012;30:83-7)

Key words: *lupus erythematosus, toxic epidermal necrolysis*

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the presence of autoantibodies that can cause tissue damage in multiple organs. The skin is the second most commonly affected organ involved in SLE.¹ Gilliam and Sontheimer proposed a classification of cutaneous lupus erythematosus (CLE) into lupus specific (acute CLE, subacute CLE, chronic CLE) and lupus non-specific CLE based on the presence of histological interface dermatitis.² CLE frequently presents without systemic internal organ involvement. However, acute CLE (ACLE) is mostly associated with systemic organ involvement.¹ ACLE can be categorized into localized ACLE, generalized ACLE and toxic epidermal necrolysis-like ACLE.² The last condition is very rare and usually fatal.

Toxic epidermal necrolysis (TEN) is a life-threatening condition resulting in an acute erythematous blistering eruption.³ The majority of cases appear to be related to idiosyncratic drug reactions.⁴ However, in some cases, it has also been reported in association with acute graft versus host disease (GVHD),⁵ infection,⁶ vaccinations⁷ and SLE.⁸ TEN is thought to be more prevalent in SLE.⁹

TEN that occurs in SLE patients has been infrequently reviewed in the previous literature.¹⁰⁻¹¹ This condition is complicated to diagnose because medication can produce a blistering eruption that resembles vesiculobullous disease in SLE. Here the authors described two cases of newly diagnosed SLE that had cutaneous presentation compatible with TEN-like ACLE.

Case reports

Case 1

A 35 year-old woman presented in April 2010 with a two-week history of progressive development of painful, targetoid erythema with an area of sheet-like desquamation on the face, V-neck area, back,

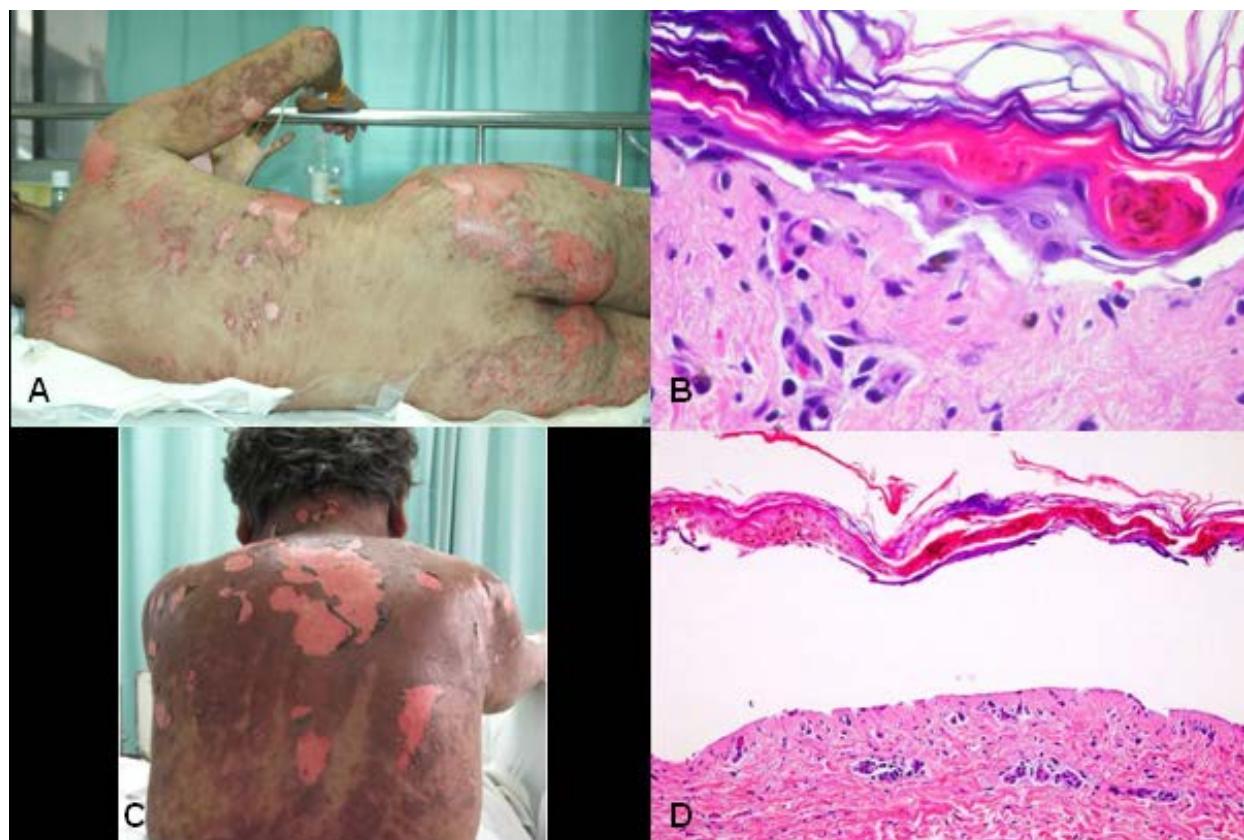


Figure 1. Patient 1(A, B) A= Erythema, sheet-like desquamation on trunk and extremities B= Interface dermatitis, subepidermal cleft, necrotic keratinocytes and almost full thickness epidermal necrosis. (Haematoxilin-eosin, original magnification $\times 60$) Patient 2 (C, D) C= Erythema, sheet-like desquamation on neck, back and extremities D= Subepidermal separation with sparse dermal infiltration. (Haematoxilin-eosin, original magnification $\times 4$)

buttocks, sacral parts and all extremities involving 30% of body surface area (BSA). (Figure 1A) There were erosions on the hard palate and lips. Periungual telangiectasia was detected on both hands and feet. Eye and genital examination were unremarkable. Her previous medical history included photosensitivity, alopecia and arthralgia of interphalangeal joints of the hands, wrists, elbows and knees. Her underlying disease was hypertension which had been controlled with amlodipine 10 mg/day for two years. No relevant medications had been newly introduced.

A skin biopsy from left thigh revealed basal vacuolization and numerous necrotic keratinocytes with subepidermal cleft. Dermal infiltration was composed of sparse lymphocytes, histiocytes, red blood cell (RBC) extravasation and melanophages. (Figure 1B) Direct immunofluorescence studies showed positive immunoglobulin (Ig) G, IgM and C3 deposition in the basement membrane zone in a granular pattern. Laboratory investigations demon-

strated microcytic anemia (Hb 7.6 g/dl, Hct 21.6%, MCV 61.2 fl), leukopenia (white blood cell (WBC) 2,130/mm³, normal $> 4,000/\text{mm}^3$), lymphopenia (489/mm³, normal $> 1,500/\text{mm}^3$) and a normal platelets count. The ANA titer was positive at a titer of 1:2560 (homogenous and peripheral pattern), the anti-dsDNA titer was 1:640, the anti-Ro (SS-A) was positive and anti-La (SS-B) was negative. C3 and C4 levels were markedly low at 38.3 mg/dl (83-177 mg/dl) and 6.94 mg/dl (15-45 mg/dl), respectively. Protein, dysmorphic RBCs and WBCs were detected on urinalysis. Lupus nephritis type IV was diagnosed from a kidney biopsy seven months afterwards. Blood chemistry showed hypoalbuminemia (albumin 1.4 g/dl, normal range 3.5-5.5 g/dl) with normal level of bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase. A herpes simplex virus antigen (HSV Ag) immunofluorescence study on tissue from the lips was negative. An electrocardiogram and echocardiography were done

Table1. Characteristics of two patients presenting with TEN-like ACLE and SLE

	Case 1	Case 2
Age, years/sex	35/Female	60/Female
Initial presentation	Erythematous patches on face, v-neck, back, limbs (BSA* 30%) malar rash, oral ulcer, periungual erythema, alopecia, photosensitivity	Erythematous macules on face, v-neck, back, limbs (BSA* 30%), blistering eruption on back, oral ulcer, periungual telangiectasia, alopecia
Onset of blistering eruption after initial presentation	two weeks	five days
Eye/genitalia involvement	None	None
Internal organ involvement	Lupus nephritis, acute myocarditis	Serositis, proteinuria, hematologic
History of drug ingestion/infection/vaccination (duration)	Amlodipine (2 years)	Ampodipine (2 months) Omeprazole (2 months)
Associated conditions	Hypertension	Hypertension, chronic kidney disease, anemia of chronic disease
Hematologic abnormalities	Microcytic anemia, leukopenia, lymphopenia	Microcytic anemia, leukopenia, lymphopenia
Kidney abnormalities	Proteinuria 4+, dysmorphic RBC, WBC	Proteinuria, uremia
Antinuclear antibodies (ANA)	1:2560 (homogenous and peripheral)	1:2560 (homogenous and peripheral)
Anti-dsDNA	1:640	1:640
Anti-Ro/La	Positive/Negative	Positive/Negative
C3 (normal, 83-177mg/dl)	38.3 mg/dl	19 mg/dl
C4 (normal, 15-45 mg/dl)	6.94 mg/dl	12.2 mg/dl
Histopathology of skin lesion	Basal vacuolization with numerous necrotic keratinocytes, sparse lymphocytic infiltration in dermis	Full-thickness epidermal necrosis with separation, sparse lymphocytic infiltration in dermis
Direct immunofluorescence study	IgG, IgM and C3 deposition at basement membrane	IgG, IgM and C3 deposition at basement membrane, blood vessels, appendages
Treatment	Dexamethasone 15-20 mg/day, than tapered to prednisolone 15 mg/day, chloroquine 250 mg/day	Dexamethasone 20 mg/day then tapered to prednisolone 60 mg/day, chloroquine 250 mg/day
Results	Improved	Improved

*BSA, body surface area

to exclude acute myocarditis and these demonstrated global cardiac hypokinesia. Eventually, based on clinical, histological, laboratory and autoimmune findings, SLE with TEN-like cutaneous presentation was diagnosed.

The patient was admitted and treated with dexamethasone 5 mg intravenous every 8 hours with gradual tapering. Wound dressings with petrolatum over denuded area were applied and the cutaneous symptoms markedly improved. The eroded skin healed within two weeks and the patient was discharged with prednisolone 15 mg/day, chloroquine 250 mg/day, carvedilol, enalapril and furosemide for cardiologic symptoms. No cutaneous symptoms have recurred to date.

Case 2

A 60 year-old woman presented in July 2010 with erythematous macules on her arms, legs, face and back for two days. The lesions evolved into a blistering eruption three days afterwards. Physical examination revealed generalized discrete and confluent erythematous macules and patches with areas of central dusky red on the V-neck, trunk, both arms and legs, with bullae and sheet-like desquamation involving 30% of the body surface area. (Figure 1C) Oral ulceration on the hard palate, periungual telangiectasia and diffuse thinning of hair with a positive hair pulling test were detected. Eye and genital examination were unremarkable. Her medical history also included hypertension, chronic kidney disease stage III and anemia of chronic disease for one year. Her recent medication was amlodipine, omeprazole, folic acid and FeSO₄ which had been taken for two months.

A skin biopsy from the left arm revealed full-thickness epidermal necrosis, an area of re-epithelialization with basal vacuolization and a subepidermal cleft. Sparse lymphocytes and melanophages were scattered in the dermis. (Figure 1D). Direct immunofluorescence studies showed granular IgG, IgM and C3 deposits in the basement membrane zone, blood vessel walls and appendages. Laboratory investigations demonstrated anemia (Hb 8.3 g/dl, Hct 25.3%, MCV 78 fl), leukopenia (WBC 2,400/mm³), lymphopenia (348/mm³) with a normal platelets count. The direct Coombs' test was negative. The ANA titer was positive at a titer of 1:2560 (homogenous and peripheral pattern), the anti-dsDNA titer was 1:640, the anti-Sm was positive, the anti-Ro (SS-A) was positive and the anti-La (SS-B) was negative. C3 and C4 levels were low with 19 mg/dl and 12.2 mg/dl respectively.

Urine protein 24 hours was 0.61 g/day (normal < 0.3 g/day). The chest X-ray showed bilateral pleural effusions. Ultrasound-guided thoracocentesis showed evidence of an exudative profile. A positive ANA at a titer of 1:2560 with a homogenous pattern was detected from the pleural fluid.

A diagnosis of SLE with a cutaneous presentation that resembled TEN was made. Dexamethasone 5 mg intravenous every 6 hours was prescribed for both TEN and SLE for three days, then tapered to prednisolone 60 mg/day, in combination with chloroquine 250 mg/day. All desquamated cutaneous lesions became dry and normal looking within three weeks. The organs involvement described above has remained under control since her discharge.

Discussion

Both of the present cases were newly diagnosed SLE. The subacute-onset with a blistering eruption and widespread sheet-like desquamation combined with the histological changes of apoptosis of the epidermis were compatible with a diagnosis of TEN. The differential diagnosis of drug-induced TEN and other vesiculobullous disease in SLE has been considered. However, there was no evidence of high risk drugs, infections, GVHD and vaccination and oral cavity was the only mucosa site involved. From these features, the authors suggest the diagnosis of TEN-like ACLE in both cases.

Mandelcorn et al.⁸ described the term ‘lupus-associated TEN’ (L-ATEN) in two cases which had subacute development of idiopathic TEN with underlying SLE. Slow progression of the blistering eruption, absence of systemic features, lack of evidence of high risk drug ingestion and positive autoimmune serology were the factors that differentiated this condition from classic TEN. Paradela et al. reported a case that combined feature of ACLE and drug-induced TEN.¹² This emphasizes the difficulties in recognizing TEN-like LE and drug-induced TEN.¹² Moreover, Ting et al. coined the term “Acute syndrome of Apoptotic Pan-Epidermolysis (ASAP)” for a clinical syndrome of life-threatening and massive cleavage of the epidermis from a hyperacute apoptotic injury that can occur in a setting other than that of drug hypersensitivity (e.g., LE, acute GVHD, pseudoporphyria).¹³ SLE predisposition, ultraviolet light, photodistribution area and less prevalence of mucosal involvement were the differentiating factors from classic TEN.¹³ Compared to the present

cases, they had features of subacute progressive cutaneous lesions, less mucosal involvement, SLE and positive autoimmune profiles that support the diagnosis of this rare condition. From this data, it should be noted that TEN-like ACLE could be a factor in the development of SLE.

Drug-induced TEN has been frequently reported. In case 2, the previous history of amlodipine, omeprazole, FeSO₄, and folic acid ingestion had been initially suspected to be the cause of the TEN. However, amlodipine, FeSO₄ and folic acid have not been reported to be the cause of TEN, but it can be caused by omeprazole, as previously reported.¹⁴ Generally, the typical duration from the beginning of the drug usage to the onset of a reaction ranges from one to three weeks.¹⁵ The second case had been taking the medication for two months. In drug-induced lupus, clinical manifestations resemble SLE, but cutaneous and renal manifestations are rare in this group. The symptoms usually develop more than a year after starting the medication.¹⁶

The standard treatment of TEN-like ACLE remains controversial. In previous case reports, corticosteroids have been shown to have beneficial effects^{8,11-13,17} and IVIG is also helpful.^{8,10} Plasmapheresis was successful in one case report.¹⁸ Corticosteroids were prescribed in the present cases due to continuing lupus activity and produced favorable results. Chloroquine was combined for its immunomodulatory effect.

In conclusion, the authors have described two cases presenting with TEN-like ACLE which occurred in the context of systemic involvement of SLE. Both cases had satisfactory responses to corticosteroids. The cutaneous lesion was gradually progressive, with little mucosal involvement and was mainly photodistributed. The authors suggest that the complexity and rarity of this condition could be related to variations in the systemic severity of SLE.

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