

## CLINICAL REPORT

# Toxic Epidermal Necrolysis-like Cutaneous Lupus Erythematosus: A Series of Three Patients

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**Toxic epidermal necrolysis-like lesions have been described in the setting of lupus erythematosus, and have been considered as a specific hyperacute variant of cutaneous lupus erythematosus, with features different from classical drug-related toxic epidermal necrolysis. We report here a series of three patients with lupus erythematosus who presented with severe worsening of their cutaneous disease in a toxic epidermal necrolysis-like fashion. We compared these cases with cases reported previously. Based on this discussion, we speculate that some of these patients may have classical drug-related toxic epidermal necrolysis rather than lupus erythematosus-related toxic epidermal necrolysis. Key words: drug-induced skin reactions; cutaneous lupus erythematosus; toxic epidermal necrolysis; apoptosis.**

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Bullous lesions in the context of lupus erythematosus (LE) have been recognized in different clinical settings with variable significance. Several publications have focused on the subject of a toxic epidermal necrolysis (TEN)-like presentation of acute or subacute LE in regard to its characterization, differential diagnosis compared with classical TEN, and prognosis (1–4). The TEN-like presentation of LE is believed to occur in patients with

subacute or acute cutaneous LE that typically develops features of TEN with unusual subacute progression and apparent absence of high-risk drug ingestion. The term “acute syndrome of apoptotic pan-epidermolysis” (ASAP) has been proposed to include distinct settings of massive apoptotic injury of the epidermis resulting in life-threatening massive shedding (drug-induced, LE, graft versus host disease, pseudoporphyria) (2).

We describe here the cases of three additional LE patients who developed TEN-lesions during the course of their disease. As the clinical features and outcomes of these patients were not uniform, we also discuss the possible diagnosis of classical TEN in one of them.

## CASE REPORTS

Clinical and laboratory findings, and treatment details of the patients are shown in Table I. All patients were young women previously diagnosed with systemic LE. The interval from initial diagnosis of LE to development of TEN-like lesions varied from 45 days to one year. All 3 patients initially presented with typical lesions of subacute or acute cutaneous LE that showed a somewhat distinct erosive character. These lesions failed to improve with classical treatment with oral corticosteroids and chloroquine diphosphate. Instead, they progressively worsened, with the development of innumerable confluent erythematosus and purpuric macules with superficial necrosis and blisters that culminated into large bullae. These were initially restricted to the areas of lupus lesions, but during evolution they

Table I. Characteristics of three patients with toxic epidermal necrolysis-like lupus erythematosus. All patients had normal kidney function and serum complement levels

Patient/ age/sex	Initial presentation	Serological abnormalities	Haematological abnormalities	Previous treatment	Mucosal lesions	Time	Treatment	Outcome
1/23/F	SCLE	ANA-1:320 nucleolar anti-RO + anti-LA +	rbc 3920 wbc 2400	Chlor. 250 mg/day Pred. 40 mg BID pulse Pred. 40 mg BID pulse	No	45 days	Chlor. 250 mg/day Pred. 60 mg/day Aza. 150 mg/day	Improved
2/19/F	ACLE	ANA-1:1280 homogenous anti-DNA +	rbc 3900 wbc 3770	Chlor. 250 mg/day Pred. 40 mg/day	No	3 months	Chlor. 250 mg/day Pred. 60 mg/day	Improved
3/17/F	SCLE	ANA- 1:1280 speckled anti-DNA + anti-Sm + anti-RNP +	rbc 3600 wbc 3460	Chlor. 250 mg/day Pred. 40 mg/day	Yes	1 year	Chlor. 250 mg/day Pred. 60 mg/day	Death from sepsis

SCLE: subacute cutaneous lupus erythematosus; ACLE: acute cutaneous lupus erythematosus; rbc: red blood cells/ $\mu$ l (normal range 4400–5900/ $\text{mm}^3$ ); wbc: white blood cells/ $\mu$ l (normal range 4000–11000/ $\text{mm}^3$ ); Chlor: chloroquine diphosphate; Aza.: azathioprine; Pred.: prednisolone

progressed to previously unaffected areas. After a few days the lesions began to shed; extensive denuded areas of epithelial loss identical to TEN were then observed (Figs 1 and 2). Oral mucosal lesions were observed only in patient 3 (Fig. 2). Patients 1 and 2 slowly improved with treatment; the course in patient 3 was fulminant, and she died from sepsis after a few days.

Histopathology of pre-existent lesions revealed an interface dermatitis typical of LE in all patients. Histopathology of later developed lesions showed extensive epidermal necrosis and subepidermal cleavage. Necrotic keratinocytes, as well as perivascular and interstitial inflammatory neutrophilic infiltrate with areas of basal layer damage were present (Fig. 3a, b). In addition, necrotic keratinocytes in the acrosyringea were seen in patient 3 (Fig. 3d). Direct immunofluorescence revealed immunoglobulin (Ig)M, IgG, IgA, and C3 fluorescence in the basement membrane zone. Dermal vessels showed C3 in patients 2 and 3 (Fig. 3e, f).

## DISCUSSION

Blistering dermatoses in the setting of systemic LE (SLE) have long been recognized, and most of these have been grouped into the broad designation of "bullous SLE" (2). Otherwise, "bullous LE" also designates the specific non-scarring eruption with tense, clustered blisters on sun-exposed areas occurring on patients with active LE, which is characterized microscopically by neutrophilic infiltrates in the dermal papillae (5).

Sontheimer (6) classified vesicobullous lesions occurring in the setting of LE in specific (diagnostic) and non-specific (non-diagnostic) forms. Specific vesicobullous lesions occur as a result of aggressive inflammatory epidermal basal layer damage, occurring as a dramatic extension of the interface dermatitis (2, 6). Five types of blistering presentations are included:

- TEN-like acute cutaneous LE: sheet-like cleavage of skin changes rapidly evolving from pre-existing photodistributed confluent acute LE lesions.
- TEN-like subacute cutaneous LE: sheet-like cleavage of skin changes evolving from otherwise typical photodistributed non-scarring annular or papulosquamous lesions in association with anti-Ro/SS-A: La/SS-B.
- TEN occurring in SLE patients not having conventional LE-specific skin lesions.
- Vesiculobullous changes occurring at the active border of advancing of annular SCLE.
- Vesiculobullous chronic cutaneous LE.

The LE non-specific skin lesions do not exhibit interface dermatitis and can be seen in clinical settings other than LE (e.g. dermatitis herpetiformis-, epidermolysis bullosa acquisita-, and bullous pemphigoid-like LE) (2, 6). Curiously, Sontheimer (6) does not clearly include the aforementioned "bullous LE" in any of the above categories. Lee & Ackerman (5) consider this presentation an exaggeration of the specific acute LE process on the skin, with massive neutrophil infiltration and mucin.

Our patients 1 and 2 share the clinical features of the previously described cases of TEN-like LE, and their TEN-like lesions developed from subacute and acute LE lesions, respectively. There were no mucosal lesions. Clinical course was subacute and they improved with treatment. Patient 3 had typical annular subacute cutaneous LE, and her TEN-like lesions were initially observed to occur over the pre-existing annular lesions. In contrast to patients 1 and 2, however, the progression of her eruption was fulminant and devastating. New lesions developed in a few days with massive epidermal shedding; there were severe mucosal erosions, and she died from sepsis despite treatment and support. Ting et al. (2) suggest that mucosal involvement may be less severe in TEN-like LE than in classical TEN.

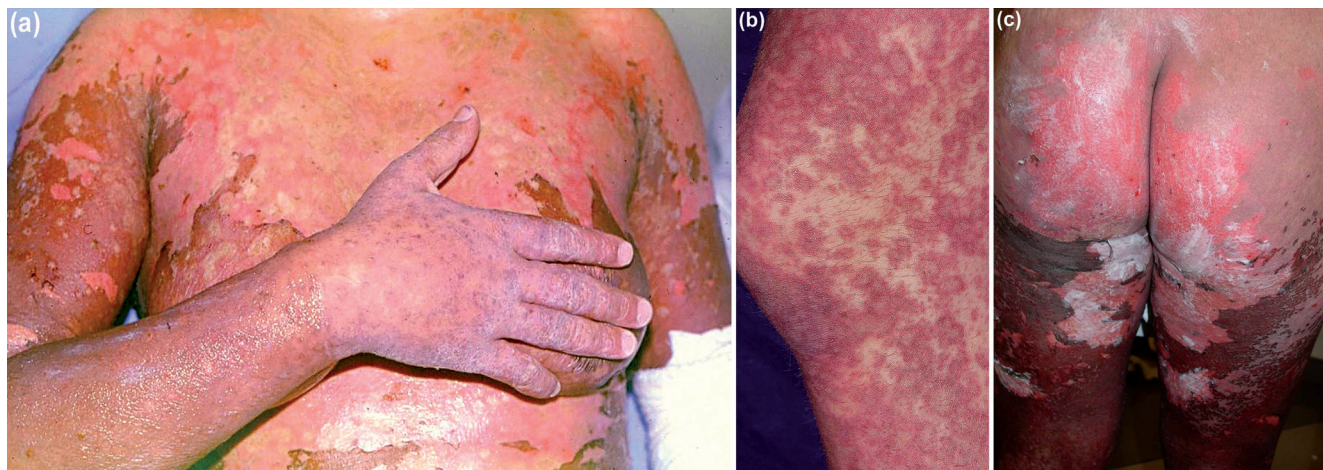


Fig. 1. (A) Patient 1: Well-established toxic epidermal necrolysis lesions (TEN). (B) Patient 2: Incipient TEN with erythematopurpuric macules and blisters. (C) Patient 2: Extensive denuded areas.

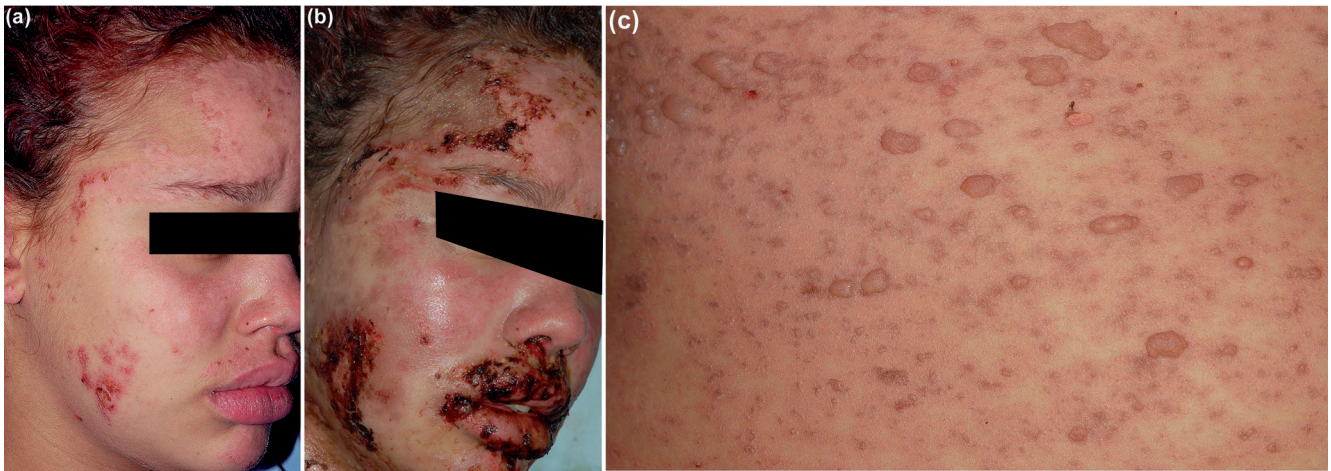


Fig. 2. (A) Patient 3: lesions of polycyclic subacute cutaneous lupus erythematosus. (B) One week after development of toxic epidermal necrolysis (TEN) lesions. Notice progression of subacute lupus erythematosus lesions to TEN lesions. (C) Detail of confluent erythema and blisters of evolving TEN.

The possibility of a drug reaction could not be discounted in any of the patients since they were in the dermatology ward for a number of days before worsening of their eruption and they were taking several medications including analgesics and antibiotics. Nonetheless, patients 1 and 2 showed a subacute clinical course that parallels the previously described cases of TEN-like LE, while patient 3 behaved more like classical TEN. Otherwise, observation of Fig. 3a and b reveals progression of typical subacute LE to TEN-like lesions in patient 3. Definitive differential diagnosis may be impossible, since histopathological, serological, and immunofluorescence markers were almost identical in all cases. The presence

of apoptotic keratinocytes on the acrosyringia on biopsy of patient 3 may suggest drug-induced TEN (7).

The term “acute syndrome of apoptotic pan-epidermolysis” (ASAP) was proposed to include all the clinical situations of massive and acute epidermal cleavage resulting from apoptotic injury. ASAP, then, comprises drug-induced TEN, TEN-like LE, and other conditions as acute graft versus host disease and TEN-like pseudoporphyria (2). The three cases described here demonstrate the difficulty of distinguishing between these situations and their variable clinical course.

*The authors declare no conflict of interest.*

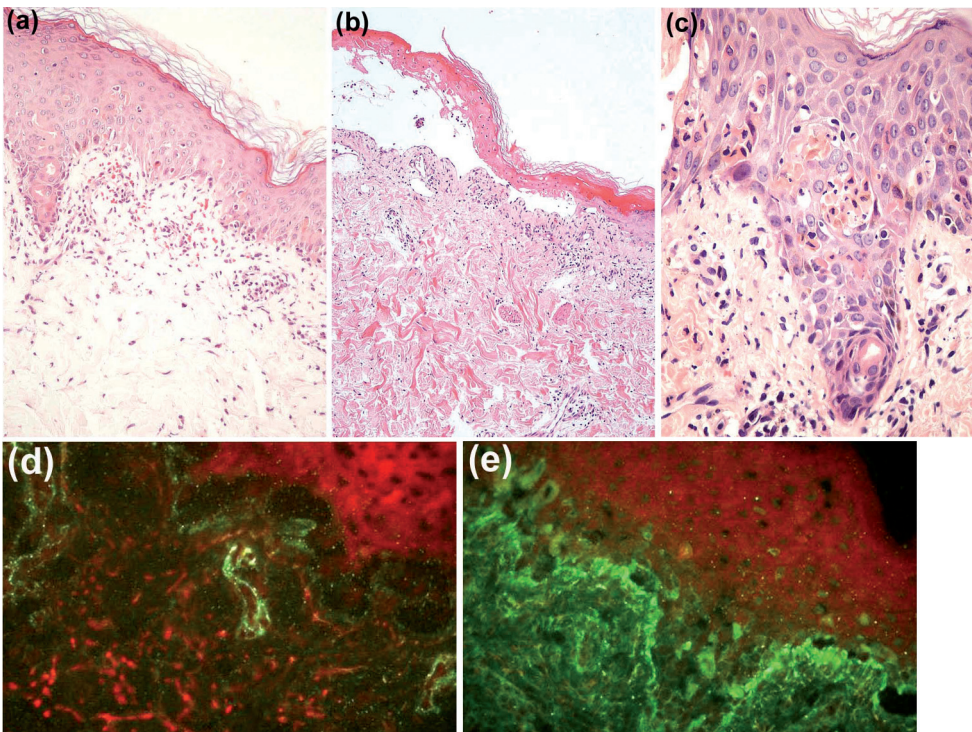


Fig. 3. (A) Patient 1: Very incipient aspect. Scattered necrotic keratinocytes on the epidermis with superficial perivascular inflammatory infiltrate (haematoxylin-eosin (HE) original magnification  $\times 100$ ). (B) Patient 2: Well-established lesion. Extensive epidermal necrosis (HE  $\times 100$ ). (C) Many necrotic keratinocytes on the acrosyringia (patient 3) (HE  $\times 200$ ). (D) Direct immunofluorescence-IgM positivity on dermal vessels. (E) Direct immunofluorescence-IgG positivity on basal membrane zone.

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