Toxic epidermal necrolysis-like acute cutaneous lupus erythematosus: report of a case and review of the literature

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Abstract

Severe bullous eruptions in systemic lupus erythematosus (SLE) patients include bullous SLE, Rowell syndrome, toxic epidermal necrolysis (TEN), and TEN-like eruption of acute cutaneous lupus (TEN-like ACLE). TEN-like ACLE, a rare manifestation of SLE that closely mimics TEN, can be distinguished by characteristic clinical and laboratory findings. A 27-year-old man with SLE who developed TEN-like ACLE after initiating mycophenolate mofetil for active SLE is reported. The reports of 37 women and six men — including our patient — with TEN-like ACLE were also reviewed. The diagnosis of SLE or subacute cutaneous lupus erythematosus was either previously confirmed or established at the time of diagnosis of TEN-like ACLE in 41 patients. Fever was present in 59% of patients. The onset of TEN-like ACLE was either subacute (73%) or acute (27%). Thirteen cases did not clarify the nature of disease onset. The skin lesions often presented initially on sun-exposed sites (29 patients) and involved one or more mucous membranes (21 patients). A new medication may have caused the TEN-like ACLE in 67% of the patients. Systemic corticosteroids — either alone or combined with hydroxychloroquine, intravenous immunoglobulin, or mycophenolate mofetil — were the most commonly used treatment. Patients with TEN-like ACLE patients had an 89% survival.

Keywords: acute, bullous, eruption, drug rash, mycophenolate mofetil, systemic lupus erythematosus, toxic epidermal necrolysis

Introduction

The acute syndrome of apoptotic pan-epidermolysis (ASAP) shares features of massive epidermal cleavage and necrosis caused by acute apoptotic basal layer injury [1]. Toxic epidermal necrolysis-like acute cutaneous lupus erythematosus (TEN-like ACLE), a rare manifestation of systemic lupus erythematosus (SLE), is an ASAP. It presents as widespread denudation and blistering of skin mimicking toxic epidermal necrolysis (TEN) clinically and histologically; however, it occurs in patients with hyperacute SLE. Other entities in this group of ASAP include TEN-like graft-versus-host disease (GVHD) and TEN-like pseudoporphyria.

The proposed mechanisms of pathogenesis for the massive apoptotic injury shared by both ASAP entities (such as TEN-like ACLE) and TEN may explain why these diseases closely resemble each other. They include not only increased interleukin 6 and interleukin 10 (in both TEN-like GVHD and TEN [2]), but also include upregulation of Fas and Fas-Fas ligand interactions (in both TEN-like ACLE and TEN [3-5]). In addition, postulated mechanisms for the etiology of keratinocyte apoptosis in both TEN and SLE demonstrate a role for cytotoxic and/or autoimmune T cells, with cytokine release and subsequent amplification of the inflammatory cascade [5-7].

However, the pathogenesis of TEN and SLE involve additional distinguishing factors. TEN is associated

with specific haplotypes affecting drug metabolism, such as HLA B* 1502 and HLA B* 5801, increasing the risk of TEN with ingestion of carbamazepine [8] and allopurinol [9]. TEN risk is also increased by infection with specific agents, including HIV [10] and mycoplasma [11]. In addition, granulysin — found in 2-4 times higher levels than perforin and soluble Fas ligand — is the most critical cytotoxic molecule in TEN-induced apoptosis [12].

In contrast, in SLE, ultraviolet light is considered a primary driver of disease activity; it induces apoptosis and necrosis, which results in an increase in the levels of chemokine CCL27. Subsequently, activation of autoimmune T cells and plasmacytoid dendritic cells occurs [6-7].

A patient with TEN-like ACLE, a 27-year-old man with SLE, is reported. The clinical differential diagnosis of bullous eruptions in SLE patients is discussed [1, 13-17]. Also, the literature of all biopsy-proven reported patients with TEN-like ACLE is reviewed.

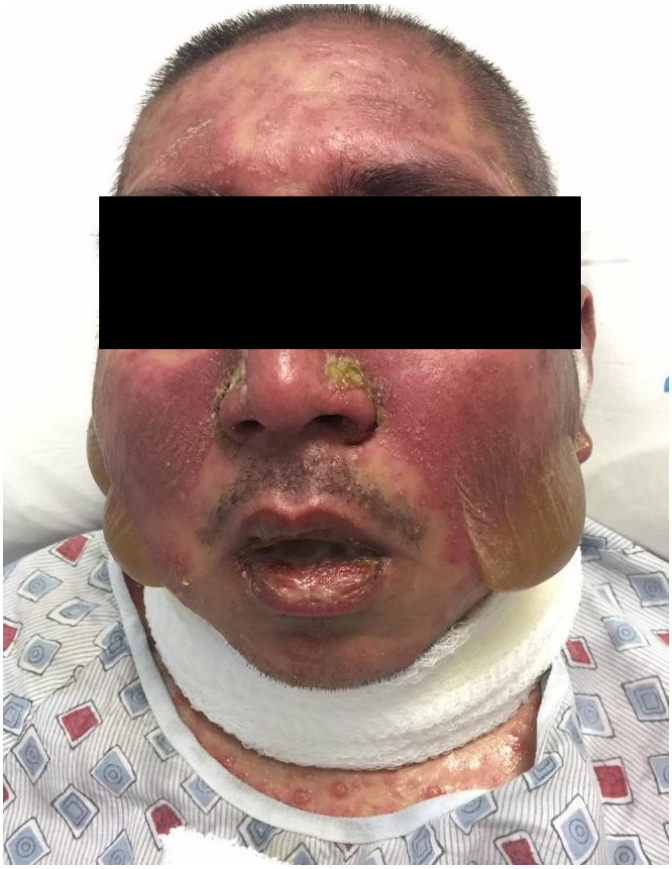

Figure 1.*A distant view of the patient's face shows facial edema, erythematous plaques, mucosal involvement, and tense bullae.*

Case Synopsis

A 27-year-old man presented to the emergency department for a pruritic rash that began on his forehead and ears but subsequently spread to his chest, upper back, arms, and mouth over the course of one day. His past medical history was significant for SLE, diagnosed 1.5 years ago, with malar rash, arthralgia, hypocomplementemia, transaminitis, and positive antibody studies: antinuclear antibody (ANA), anti-double stranded DNA antibody, anti-Smith antibody, anticardiolipin antibodies, lupus anticoagulant antibodies, and Sjogren syndrome A (Ro) antibody. He was treated with hydroxychloroquine and low-dose prednisone and appeared to do well. However, he developed a deep vein thrombosis three months later and warfarin was added to his regimen.

Seventeen days prior to emergency room presentation, he was seen by his rheumatologist and noted to have malar rash, diffuse non-scarring alopecia, arthralgia, and the new-onset of visual changes suggestive of cerebritis. Since his active SLE

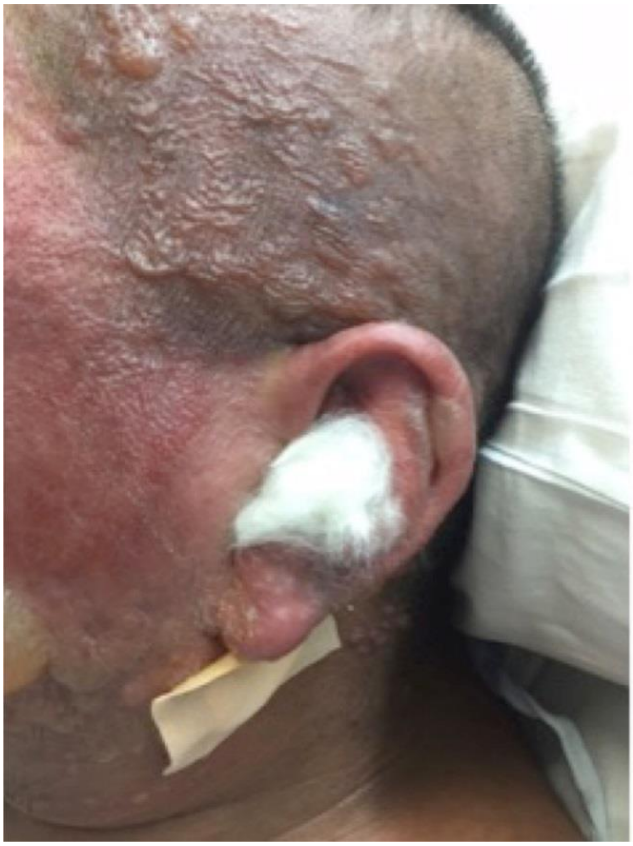

Figure 2. *Additional bullae are present on the left parietal scalp, helix, and antihelix.*

required additional therapy, mycophenolate mofetil was added to his regimen as efficacy has been demonstrated in several studies [18-24].

In the emergency room, his vital signs were normal. He denied fever, malaise, arthralgia, or painful skin. His medications included warfarin (for deep vein thrombosis prevention), lisinopril and hydrochlorothiazide (for longstanding hypertension), tramadol (for chronic back pain), and prednisone, hydroxychloroquine, and mycophenolate mofetil (for SLE).

Mucocutaneous examination showed erythematous edematous plaques on the nasal bridge and malar cheeks, small vesicles along both helical rims and the left palate of the oral cavity, and a faint morbilliform eruption on the sun-exposed areas of his upper trunk and proximal arms. The Nikolsky sign was negative.

The photodistributed erythematous patches and the oral eruption were interpreted as bullous SLE. His daily dose of prednisone was increased and triamcinolone ointment 0.1% was prescribed for twice daily application to the affected areas. All of his current medications were continued.

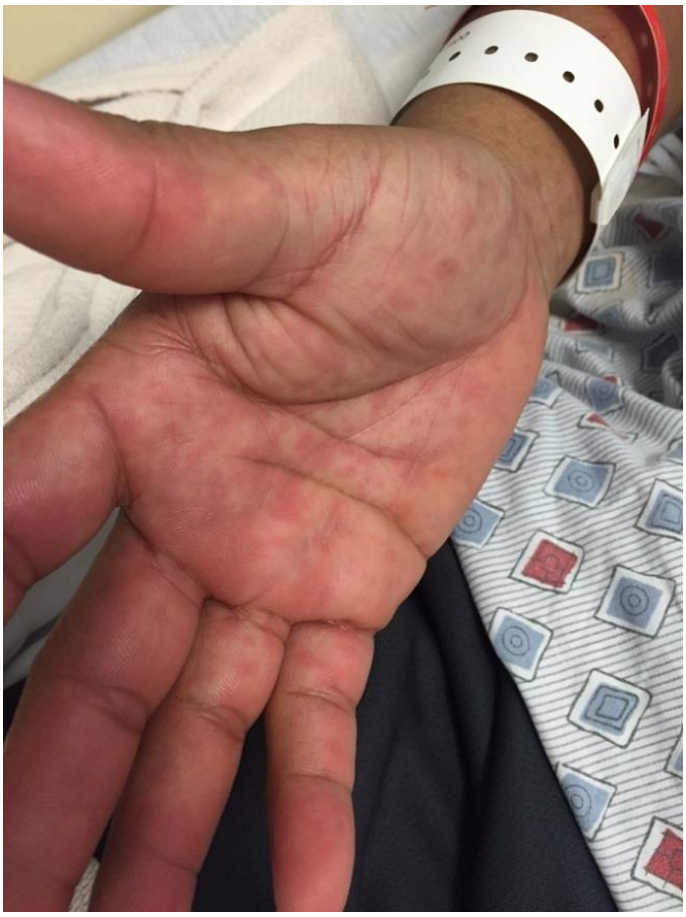

Figure 3.*The right palm shows erythematous macules and patches.*

The patient returned to the emergency department the following day; his rash was markedly worse. Examination of his skin and mucosal membranes showed tender, infiltrated plaques on the face, tense bullae on the ears and in the oral cavity, erosions on the vermillion lips, and erythematous macules and papules on the upper trunk and proximal extremities (**Figures 1, 2**). The palms and soles demonstrated erythematous macules and papules (**Figure 3**); his penis had a small erosion. He was afebrile with normal vital signs. He was admitted to the hospital for further workup; all of his medications were stopped.

Laboratory abnormalities included the following: mild leukopenia (white blood cell count of 4,600 per cubic milliliter, normal 4,800 to 10,800), elevated C-reactive protein (0.95mg per liter, normal <0.8), elevated liver enzymes (aspartate aminotransferase = 39 IU per liter, normal 10 to 25 and alanine aminotransferase = 51 IU per liter, normal 10 to 40), and a decreased platelet count of 101,000 per cubic milliliter (normal 140,000 to 400,000). Additional studies, ordered two days later, showed active SLE. He had an elevated anti-double stranded DNA antibody of 88.6 IU per milliliter (normal 0 to 25) and an elevated anti Ro (Sjogrens syndrome A) antibody of 149 EU per milliliter (normal 0-16). Anti La (Sjogrens syndrome B) antibody was normal at 2.7 EU per milliliter (normal 0-16).

Skin biopsies were taken from the right thigh and right neck for hematoxylin and eosin staining. Microscopic examination of the skin biopsy from the right thigh showed near confluent dyskeratotic keratinocytes, some in collections, not only along the dermoepidermal junction but also extending down adnexae and scattered at higher levels within the epidermis (**Figure 4**). Scattered neutrophils and neutrophil dust were present in the papillary dermis. Also, there was a superficial and deep perivascular and periadnexal infiltrate of lymphocytes with occasional eosinophils. The right neck biopsy showed similar pathologic changes; in addition, subepidermal bullae formation was present (**Figures 5, 6**).

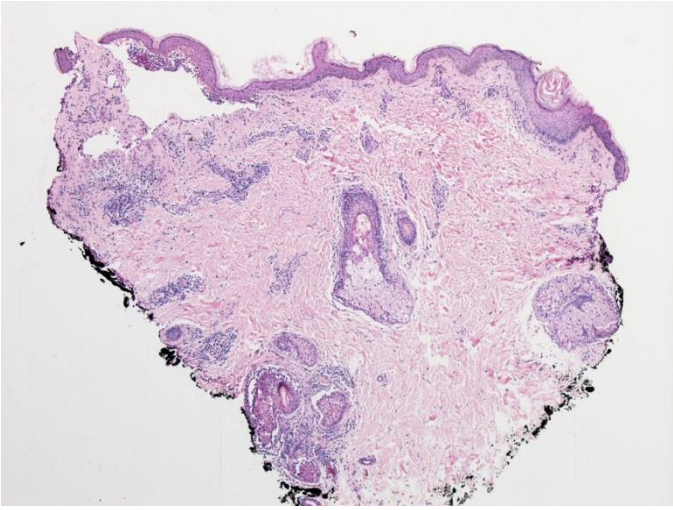

Figure 5. *Microscopic examination of the biopsy of the right neck shows a subepidermal bullae with underlying superficial and deep perivascular inflammation (H&E, 4×).*

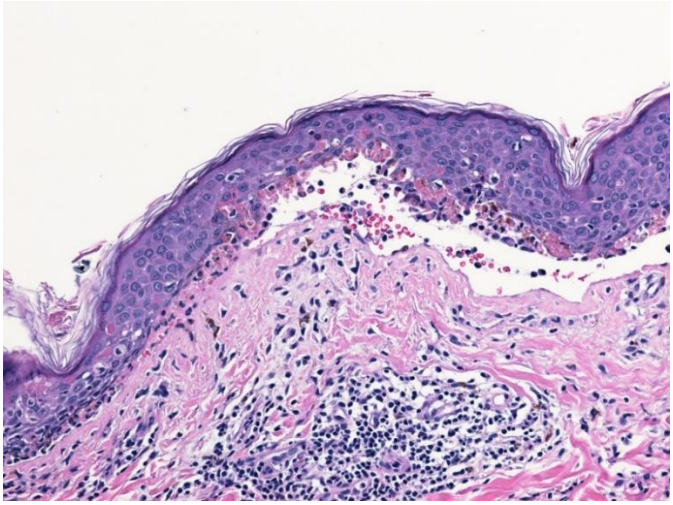

Figure 6. *Higher power view of right neck biopsy reveals confluent dyskeratosis above the bullae (H&E, 20×).*

Skin biopsies were also taken from the right chest for direct immunofluorescence (DIF) staining. The DIF staining demonstrated granular IgM, C3 and C5-9 along the basement membrane zone. There was also fine staining of IgG in the lower one third of the epidermis and along the epidermal basement membrane zone.

The hematoxylin and eosin stained biopsies were interpreted as erythema multiforme/TEN with underlying lupus erythematosus. The DIF stained biopsy was interpreted as consistent with lupus erythematosus. Correlation of the clinical history, lesion morphology, laboratory studies and pathologic finding (from both the routine and immunofluorescence staining of his skin biopsies) established the diagnosis of TEN-like ACLE.

The patient was started on intravenous methylprednisolone as well as supportive care including intravenous morphine as needed for pain, magic mouthwash, nystatin mouthwash, gentle wound care, artificial tears eye drops, moxifloxacin ear drops, prednisolone acetate eye drops, and erythromycin ophthalmic ointment. Large painful bullae were expressed for symptomatic relief. The warfarin was restarted. He was treated with intravenous methylprednisolone for seven days, followed by oral prednisone that was slowly tapered. He progressively improved and was discharged after 11 days on hydroxychloroquine, lisinopril, prednisone, and warfarin. Our patient is currently managed on hydroxychloroquine 200 mg twice daily, azathioprine 250 mg daily, prednisone 7.5 mg daily, and warfarin 10 mg daily.

Case Discussion

Bullous eruptions in SLE patients can be challenging to diagnose. Our patient presented with acute onset of vesicles and bullae in the context of SLE. The differential diagnosis of bullous eruptions in SLE patients includes bullous SLE, Rowell syndrome, TEN, and TEN-like ACLE [1, 13-14, 16, 25-46]; the clinical and pathological features for these conditions are summarized in **Table 1**, [1, 13-17].

Bullous SLE was our initial diagnosis based upon our patient's active SLE and the presentation of bullae and erythema in sun-exposed areas. However, his skin lesions progressed to involve nearly his entire body, including multiple mucosal sites, which did not support this diagnosis. Further, the biopsy demonstrated marked dyskeratosis and apoptosis (including extension down adnexae) with foci of necrosis, excluding bullous SLE.

Merklen-Djafri et al. reviewed blisters and loss of epidermis in lupus erythematosus [16]. They observed two pathologic patterns for the 22 patients in their series: classic lupus erythematosus interface dermatitis, and neutrophilic dermatosis with tense blisters and vesicles. They noted that interface

dermatitis, carried to the extreme, could result in TEN-like ACLE.

Five of Merklen-Djafri et al.'s patients met clinical criteria for TEN-like ACLE; they had an acute or prior SLE diagnosis, sheet-like detachment of skin, and (in all but one) photodistribution of their skin lesions. All five individuals demonstrated vacuolar interface dermatitis and other variable histologic features suggestive of lupus erythematosus, in addition to foci of full thickness necrosis of the epidermis. In addition, two of their patients showed neutrophils in the infiltrate, similar to our case, in addition to lymphocytes.

Rowell syndrome was also considered as a diagnostic possibility for our patient. He had a positive anti-Ro antibody, a preexisting diagnosis of SLE, and a skin biopsy showing features within the spectrum of erythema multiforme. However, his photodistributed bullous presentation, progression to full body involvement of skin lesions (including multiple mucosal sites), and only solitary episode of the dermatosis excluded this diagnosis.

TEN associated with mycophenolate mofetil was entertained, particularly given the timing of 17-day interval between initiation of mycophenolate mofetil and the onset of clinical symptoms. Mockinhaupt's study of 379 SJS/TEN patients showed an interval of four days to two months to be the most common interval between drug initiation and TEN [17]. However, mycophenolate mofetil is not a high risk drug for adverse cutaneous reactions (**Table 2**), [18-24]; indeed, to the best of our knowledge, it has not been reported to cause erythema multiforme or TEN. In fact, it has not only been used off label to treat recurrent erythema multiforme [24], but also for the management of four patients with TEN-like ACLE [13, 36].

Table 1. *Differential diagnosis of our patient's bullous eruption [1, 13-17].*

	Clinical findings	Pathologic findings	DIF
Bullous LE	Tense vesicobullous lesions on sun-exposed skin Occasionally associated with mucus membrane involvement	Subepidermal blister with neutrophils	Linear or granular IgG, IgM, IgA, and C3 at the DEJ
Rowell's Syndrome	Major criteria[a]: Presence of LE (discoid, systemic, or subacute) EM-like lesions Speckled pattern of antinuclear antibody Minor criteria: Chilblains lesions Presence of anti-Ro and/or anti-La antibodies Positive RF	Necrotic keratinocytes accompanied by subepidermal blister; mild lymphocytic infiltrate	Negative
TEN	Flu-like prodrome followed by dusky macules that coalesce; subsequent development of bullae along with epidermal sloughing >30% body surface area Severe mucous membrane involvement Most cases associated with a causative drug	Full thickness epidermal necrosis; sparse to absent lymphocytic infiltrate	Negative
TEN-like ACLE	Vesicobullous lesions with epidermal sloughing, often photoaccentuated, > 30% body surface area May have mucosal involvement, particularly oral Prior or acute diagnosis of lupus	Full thickness epidermal necrosis often with marked dyskeratosis extending down adnexae May have additional features present including interface and dermal inflammation and mucin	May find granular IgG, IgM, and/or C3 binding at the DEJ

[a] The diagnosis of Rowell's syndrome (modified criteria by Zeitoni et al. [14]) requires that all three major criteria and at least one minor criteria are met. Original criteria described by Rowell et al [15] included lupus erythematosus, erythema multiforme-like skin lesions (without known precipitating factors), and immunological abnormalities in the serum (speckled pattern of ANA, anti-La (Sjogren syndrome antigen B antibody and positive rheumatoid factor).

Abbreviations: %, percent; >, greater than; ACLE, acute cutaneous lupus erythematosus; C3, third component of complement; CLE, cutaneous lupus erythematosus; DEJ, dermoepidermal junction; DIF, direct immunofluorescence; IgA, immunoglobulin A; IgG, immunoglobulin G, IgM, immunoglobulin M; LE, lupus erythematosus; RF, rheumatoid factor; TEN, toxic epidermal necrolysis

Table 2. *Characteristics of mycophenolate mofetil [18-24].*

Indications	FDA approved for organ transplant rejection prophylaxis in cardiac, hepatic, and renal allogeneic transplants Off-label use includes EM (recurrent), GVHD, psoriasis vulgaris (chronic plaque-type), RA, SLE (refractory), and systemic vasculitis
Mechanism	It inhibits purine synthesis by blocking the de novo pathway of guanosine nucleotide production. This results in decreased DNA and RNA synthesis, which limits T-lymphocyte and B-lymphocyte proliferation
Complications	GI complaints are most common Cardiorespiratory, GU, hematologic, infectious, and metabolic adverse events are possible Malignancy may develop Cutaneous reactions are uncommon; reported dermatologic adverse events include acne, dyshidrotic eczema exacerbation, papulosquamous psoriatic-like skin eruption, and rash

Abbreviations: DNA, deoxyribonucleic acid; EM, erythema multiforme; FDA, Federal Drug Administration; GI, gastrointestinal; GU, genitourinary; GVHD, graft-versus-host disease; HSV, herpes simplex virus; RA, rheumatoid arthritis; RNA, ribonucleic acid; SLE, systemic lupus erythematosus

Our patient's presentation best fits TEN-like ACLE. He had active SLE and his vesicles and bullae were initially photodistributed. In addition, a lesion skin biopsy stained with hematoxylin and eosin showed marked dyskeratosis and necrosis with underlying features of lupus erythematosus; a skin biopsy for DIF staining was also positive for lupus erythematosus. Further, he had a rapid recovery after treatment with systemic corticosteroids was started.

Including our patient, we discovered 43 biopsy-proven individuals with TEN-like ACLE (**Table 3**), [1, 13-14, 16, 29-46]. There were 37 women and 6 men. Hence, the ratio of women to men was 6.5:1.

The patients ranged from 12 to 78 years of age at diagnosis; the mean diagnosis age was 43 years. The women ranged from 12 to 78 years of age at diagnosis (with a mean diagnosis age of 43 years) and the men ranged from 18 to 62 years of age at diagnosis (with a mean diagnosis age of 43 years).

Ethnicity was described in 17 patients. There were 11 Caucasians (cases 2, 3, 10, 14, 16, 19, 20, 22, 27, 30, 39), four Asians (cases 1, 5, 13, 25), one African American (case 8), and one Hispanic (case 43).

Many of the patients (60%) had a confirmed diagnosis of SLE (24 of 43 individuals) — by either American College of Rheumatology or Systemic Lupus International Collaborating Clinics criteria — or subacute cutaneous lupus erythematosus (SCLE, 2 individuals) prior to developing TEN-like ACLE. However, the diagnosis of SLE (in 14 patients) or SCLE (in one patient) was established at the same time as the development of TEN-like ACLE in 15 patients. The remaining two patients (who had been included in previous major reviews of TEN-like ACLE) only had cutaneous lesions of TEN -like ACLE-without a confirmed or concurrent diagnosis of SLE or SCLE when their dermatosis occurred. However, in addition to clinical and biopsy-proven TEN lesions, they also had lupus-like features (both clinically and serologically) but insufficient laboratory documentation to support SLE or SCLE.

Fever was associated with the development of TEN-like ACLE in ten patients (cases 1-3, 5, 8, 13, 19, 21, 25, 26). Seven of the patients were afebrile. The presence or absence of pyrexia was not provided for 26 of the individuals.

The clinical presentation of TEN-like ACLE was subacute (defined as the full evolution of TEN-like lesions greater than 14 days) or acute (defined as the full evolution of TEN-like lesions less than 14 days). Note that the majority of acute cases (six of eight - cases 4, 8, 9, 32, 34, 43) developed within five days. The progression of TEN-like ACLE was subacute in 22 patients and acute in eight patients. The duration of time between the onset of symptoms to the complete development of TEN-like lesions was not provided for 13 patients.

The TEN-like lesions initially appeared in sun-exposed areas in 29 of the patients; in most of these patients, the distribution of the skin lesions subsequently became widespread. However, in three patients (cases 1, 30, and 32), the skin lesions remained photorestricted. Only four patients confirmed a history of extra ultraviolet exposure or tanning bed use (cases 1, 2, 30 and 32).

The TEN-like lesions first developed in preexisting lupus skin lesions in eight of the patients (cases 4, 6, 7, 8, 21, 31, 33, and 37). Acral involvement was specifically noted in nine patients. The lesions were described as pernio in three of the patients with acral lesions (cases 1, 20, and 33).

The TEN-like lesions in 21 of the patients affected one or more mucous membranes. Indeed, 12 of these individuals had multiple mucous membrane sites. However, the majority of those with multiple mucous membranes had a limited number of lesions at each site of involvement.

The presence of a positive Nikolsky sign, detachment of the overlying epidermis when pressure is applied to the skin, was observed in five patients (cases 8, 21, 22, 30, and 40). The Nikolsky sign was absent in three patients. No information was provided regarding this clinical feature in the remaining 35 individuals.

All the patients with TEN like ACLE had skin biopsies. Pathologic findings of TEN, defined as areas of full thickness epidermal necrosis with overlying basket weave orthokeratosis of the stratum corneum, were documented in 88% (38 of 43 patients). Findings of erythema multiforme, defined as interface dermatitis with single and clustered necrotic keratinocytes both in the basal and suprabasal layers of the epidermis, were present in 12% (5 of 43 patients).

The following pathologic features were evaluated to determine if patients with TEN-like ACLE manifested background changes of lupus erythematosus: interface dermatitis, mucin, and a mild to moderate lymphocytic infiltrate. However, only biopsies that confirmed TEN-like ACLE were reviewed. Biopsies performed either prior to TEN like-ACLE eruption or at a time remote from the current TEN-like flare were excluded.

Background interface dermatitis peripheral to the area of erythema multiforme or TEN- like necrosis was exhibited by 60% (15 of 25) of the patients. Forty percent (10 of 25) of the patients did not show interface changes. Information regarding interface dermatitis was not provided for 18 individuals.

The presence of mucin was documented in 57% (8 of 14) of patients. Mucin was absent in 43% (6 of 14) of patients. The presence or absence of mucin was not commented on for 29 individuals.

A mild-to-moderate lymphocytic infiltrate was reported in 64% (18 of 28) of patients. Minimal to no inflammation was described in 36% (10 of 28) of patients. The presence of lymphocytic inflammation was not commented on for 15 individuals.

The above findings (interface dermatitis, mucin deposition in the dermis, and lymphocytic inflammation) support the concept that background features of lupus erythematosus are often present in TEN-like ACLE skin biopsies and can assist in establishing the diagnosis. These findings are in agreement with previous investigators who also found background findings of lupus erythematosus in TEN-ACLE biopsies [16, 38].

A new medication possibly provoked the TEN-like ACLE in 24 patients. A drug-eliciting etiology was initially implicated in additional patients. However, the target drug was later restarted without an adverse cutaneous event. A drug was not implicated in 12 patients. No information was provided in 7 individuals regarding a potential relationship between medication and the development of TEN-like ACLE.

Initiation of a new medication, within the four-day to eight-week time frame considered high risk for SJS/TEN, was only described in nine (cases 1, 4, 6, 7, 26, 31, 34, 39, and 43) of the 24 patients in whom a drug was implicated. In six of the nine patients within the higher risk time frame (cases 1, 26, 31, 34, 39, and 43), the drug was discontinued. Additional information was not provided regarding the patient's care plan and whether the drug was stopped in the remaining three patients (cases 4, 6, and 7).

Only one patient (case 26) received a drug, sulfasalazine, which had an associated high risk of causing TEN [17]. Five patients received drugs of moderate risk, including antibiotics (cases 1, 4, 6, and 7) and the anti-seizure medication gabapentin (case 39). In the latter patient, gabapentin had replaced carbamazepine three weeks before the onset of the rash; in addition, the patient had previously been on carbamazepine for several years.

Treatment of TEN-like ACLE included one (11 patients), two (13 patients), or greater than or equal to three (10 patients) modalities; therapy was not described for 9 patients. Systemic corticosteroids were used most commonly (32 patients) —either alone (10 patients) or combined with one or more additional therapies: most commonly hydroxychloroquine (8 patients), intravenous immunoglobulin (10 patients), or mycophenolate mofetil (four patients).

Thirty-two (89 percent) of the TEN-like ACLE patients recovered from their TEN-like lesions; in contrast, only 68 percent to 80 percent of patients with TEN survive [27, 28]. Four of the patients in our review died secondary to complications. The outcome was not described for seven patients.

Based upon our review, several observations can be summarized. First, TEN, and TEN-like ACLE have overlapping features. The diagnosis of TEN-like ACLE is often made retrospectively, after correlation of the clinical course, serologic profile, and histopathology. The skin lesions are not always photodistributed, the mucus membranes may be involved, and new medications — coincidental or potentially causative — may have been initiated prior to the onset of clinical symptoms and mucocutaneous manifestations. Also, the development of TEN-like ACLE in patients with active SLE, characterized by a state of immune dysregulation, may be triggered by ultraviolet light, infection, medications or other factors.

Second, SLE patients have been reported to have an increased incidence of TEN. However, this incidence may be inflated because of misclassification of TEN-like ACLE as TEN. Frey et al. demonstrated a relative risk of 16 for TEN in SLE patients in their United Kingdom observational study, but they suggest that misinterpretation of TEN for TEN-like ACLE may contribute to this observation [25]. However, in a more recent study of 3657 hospitalized patients in the United States, Hsu et al. found individuals with SLE to have an odds ratio of 5.34 for SJS, but an odds ratio of closer to one for TEN and SJS/TEN overlap. Perhaps the patients with TEN-like ACLE were correctly identified and excluded from this study [26].

Third, SLE patients are often on systemic corticosteroid medications. Mockinhaupt et al.'s case control European study of SJS/TEN — which included 379 patients and 1505 controls — considered corticosteroids to be a drug of moderate risk for TEN with a relative risk of 4.5 [17]. Our review did not find an association with oral corticosteroids and TEN-like ACLE. Instead, we found that there was an exacerbation of TEN-like ACLE with corticosteroid dose reduction. Specifically, TEN-like ACLE lesions were either triggered in patients who were noncompliant with their corticosteroid management (cases 9 and 18) or flared in patients who tapered their corticosteroid therapy (cases 8, 13, 25, 33, and 39).

Conclusion

TEN-like ACLE is an uncommon subtype of cutaneous lupus occurring in patients with SLE. The clinical presentation mimics TEN. Initial distribution of the skin lesions on sun-exposed sites, involvement of mucosal membranes, and exposure to a new systemic medication are frequently associated features. The morphologic differential diagnosis includes other bullous eruptions that may occur in SLE patients: bullous SLE, Rowell syndrome, and TEN. Laboratory studies (demonstrating active SLE) and pathology changes of erythema multiforme or TEN on lesion skin biopsy can help to establish the diagnosis. Biopsy changes such as interface dermatitis, lymphocytic inflammation, or mucin may be present and support the diagnosis. Including the reported patient, TEN-like ACLE has been described in 43 individuals: 37 women and six men, ranging in age from 12 years to 78 years. The diagnosis of SLE or SCLE was either previously confirmed or established

at the diagnosis of TEN-like ACLE in 41 of the patients. Fever was present in 59% (10 of 17) of patients and the onset was either subacute (22 of 30 patients) or acute (8 of 30). The skin lesions were initially photodistributed in 85% (29 of 34), involved one or more mucous membranes in 21 patients, occurred in prior lupus erythematosus skin lesions in 8 patients, and appeared on acral sites in 9 patients. The triggers involved in TEN-like ACLE remain to be definitively established; a new medication possibly provoked the TEN-like ACLE in 67% (24 of 36) of the patients. The most commonly used treatment was systemic corticosteroids — either alone (10 patients) or combined with hydroxychloroquine (8 patients), intravenous immunoglobulin (10 patients), or mycophenolate mofetil (four patients). Fortunately, most of the TEN-like ACLE patients responded readily to systemic corticosteroids and/or other immunosuppressants with an 89% survival.

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Table 3. *Review of TEN-like ACLE patients[1,2].*

Ca[3] Ref	Age Sex	Dx[4]	Onset[5]	Photo[6]	Muc[7]	Acr[8]	Bx[9]: TEN VI Mcn LI	DIF[10]	Ser[11]: ANA DsD Ro La	Drug[12]	Treatment[13]	Oc [14]
1 [29]	12 W	SLE(I)	Sub	+	Eye Lips Oral	+	+ + - +	-	+ + + +	Amp-Gent Cefaclor	Hydrox, Predn, Hc	Rec
2 [30]	14 W	SLE(I)	NA	NA	NA	NA	+ NA NA NA	NA	+ + NA NA	NA	Corticosteroid	NA
3 [13]	15 W	SLE	Sub	+	Eye Lips	NA	+ + NA +	+[15,16]	+ + NA NA	-	MP, Dapsone, IVIg, MMF	Rec
4 [31]	17 W	SLE	Acute	NA	Oral	NA	+ - NA +	+[15,17,18]	+ + NA NA	Abx, Analgscs	Chlor, Pred	Dec
5 [13]	18 M	SLE	Acute	+	Eye Lips Oral		+ + NA -	NA	NA + NA NA	-	MP, MMF	Rec
6 [31]	19 W	SLE	Sub	NA	-	NA	+ - NA +	+[15,17,18]	+ + NA NA	Abx, Analgscs	Chlor, Pred	Rec
7 [31]	23 W	SLE	Sub	NA	-	NA	+ - NA +	+[15,17]	+ - + +	Abx Analgscs	Chlor, Pred, Azat	Rec
8 [32]	24 W	SLE(I)	Acute	-	Eye Lips Oral	NA	+[19] + - +	+[16,20-22]	+ + + NA	Erythromy drops, Meds[23]	Dapsone, MP, IVIg, Plasma[24]	Rec
9 [33]	25 W	SLE	Acute	+	Oral	NA	+ NA NA NA	NA	NA + NA NA	-	Corticosteroid	Rec
10 [34]	27 W	SLE	NA	NA	NA	NA	EM NA NA NA	NA	NA NA NA NA	NA	Corticosteroid	Dec

Table 3 (continued). *Review of TEN-like ACLE patients[1,2].*

Ca[3] Ref	Age Sex	Dx[4]	Onset[5]	Photo[6]	Muc[7]	Acr[8]	Bx[9]: TEN VI Mcn LI	DIF[10]	Ser[11]: ANA DsD Ro La	Drug[12]	Treatment[13]	Oc[14]
11 [35]	28 W	SLE	Sub	+	-	-	+ - NA -	+[16,20,25]	+ + - -	-	Predn, IVIg, Plasma	Rec
12 [36]	29 W	SLE(I)	Sub	+	-	-	EM NA NA NA	NA	+ + + +	-	Hydrox, MMF, Pred	Rec
13 [29]	31 W	SLE	Sub	+	Lips Oral	-	+ - NA -	-	+ - - -	C/C	IVIg, Predn	Rec
14 [37]	31 W	SLE(I)	Sub	+	-	+	+ + NA +	+[16,26]	+ - + +	Chlor-diazepoxde	Hydrox	Rec
15 [38]	31 W	SLE	Sub	+	Anal Lips Oral	+	+ NA + +	+[27]	+ + + +brdrline	Diclofenac, Rofecoxib	NA	Rec
16 [34]	35 W	SLE	NA	+	NA	NA	+ NA NA NA	NA	NA NA NA NA	NA	Corticosteroid	Rec
17 [39]	35 W	SLE(I)	Sub	+	Lips Oral	+	+ - NA -	+[16,28]	+ + + -	Amlodipine	Dexa, Predn, Chlor	Rec
18 [33]	36 W	SLE	Sub	+	Oral	NA	+ NA NA NA	NA	NA + NA NA	-	Corticosteroid	Rec
19 [34]	40 W	SLE	NA	NA	NA	NA	+ NA NA NA	NA	+ NA NA NA	NA	Corticosteroid	Rec
20 [14]	41 W	SLE	NA	+	Oral	+	EM NA NA NA	-	+ NA - -	-	Pred, Pulsed solumedrol, Mtx, Dapsone	Rec
21 [40]	42 W	SLE	NA	+	Lips	+	+ NA NA NA	+[17,28]	- + + NA	Furosemide	Corticosteroid Cyclo	Rec

Table 3 (continued). *Review of TEN-like ACLE patients*[1,2]

Ca[3] Ref	Age Sex	Dx[4]	Onset[5]	Photo[6]	Muc[7]	Acr[8]	Bx[9]: TEN VI Mcn LI	DIF[10]	Ser[11]: ANA DsD Ro La	Drug[12]	Treatment[13]	Oc [14]
22 [41]	42 W	SLE	Sub	+	Oral	NA	+ NA NA -	-	+ NA + +	NA	CorticosteroidIVIg	Rec
23 [36]	43 W	SLE	Sub	+	-	-	EM NA NA NA	NA	+ + - -	-	Hydrox, MMF, Pred	Rec
24 [16]	46 W	SLE	NA	+	-	NA	+ + + +	+[16,28]	+ NA + NA	Diacerein	NA	NA
25 [29]	47 W	SLE	Sub	+	Eye Lips Oral	-	+ NA NA NA	+[17,29]	+ + - -	Alendronate	IVIg, Hc, Predn	Rec
26 [42]	48 M	SLE(I)	Sub	-	-	NA	+ NA NA NA	NA	+ + + NA	Sulfa, Mtx	IVIg, MP	NA
27 [34]	51 M	SCLE	NA	NA	NA	NA	+ NA NA NA	NA	+ NA + NA	NA	Corticosteroid	Rec
28 [43]	52 M	SLE	Sub	+	-	NA	+ NA NA +	+[30]	+ + + +	-	Corticosteroid IVIg	Rec
29 [38]	52 W	SLE	Sub	-	Oral	-	+ + + +	NA	+ NA + +	Valacyclovir	NA	Dec
30 [1]	53 W	SLE(I)	Acute	+	-	-	+ - NA +	+[16,31,32]	+ + + NA	Naproxen Rapebrazole	Corticosteroid IVIg	Rec
31 [44]	53 W	SCLE	Sub	+	Oral Lips	+	+ + + NA	-	+ + NA NA	Ramipril	MP	Rec
32 [45]	59 W	SCLE (I)	Acute	+	-	-	+ + NA NA	-	- NA + NA	-	Topical steroids, Corticosteroid	Rec

Table 3 (continued). *Review of TEN-like ACLE patients[1,2].*

Ca[3] Ref	Age Sex	Dx[4]	Onset[5]	Photo[6]	Muc[7]	Acr[8]	Bx[9]: TEN VI Mcn LI	DIF[10]	Ser[11]: ANA DsD Ro La	Drug[12]	Treatment[13]	Oc[14]
33 [14]	59 W	SLE	Sub	-	Oral Vlva	+	+ NA NA -	-	+ - + -	-	Pred, MP, Mtx, Dapsone[33]	Rec
34 [39]	60 W	SLE(I)	Acute	+	Oral	-	+ - NA -	+[16,28,32,34]	+ + + -	Amlodipine, Omeprazole	Dexa, Predn, Chlor	Rec
35 [16]	62 M	SLE(I)	NA	-	-	NA	+ + - +	-	+ NA + NA	Diacerin	NA	NA
36 [16]	66 W	SLE(I)	NA	+	-	NA	+ + + +	+[16,18,35]	+ NA - NA	-	NA	NA
37 [38]	67 W	SLE	Sub	+	NA	NA	+ - - +	-	+ + NA NA	A/C, cefazolin, metamizole	NA	Rec
38 [16]	70 W	ACLE	NA	+	-	Vlva	+ + - +	+[36]	+ NA + NA	Cyclo, Trastzmb, Docetaxil	NA	NA
39 [46]	72 W	SLE(I)	NA	NA	+	-	+ + + -	+[16,28,37]	+ - - -	Carb, Gabapentin, Statin	IV MP, IV abx	Rec
40 [41]	76 W	SLE(I)	Sub	NA	Gen Oral	NA	+ NA NA -	-	+ - + -	NA	Corticosteroid(pred), IVIg	Rec
41 [16]	78 W	SLE(I)	NA	+	-	NA	+ + + +	-	+ NA + NA	Sulbutiamin	NA	NA
42 [38]	78 W	ACLE	Sub	+	NA	NA	+ - + -	-	NA NA NA NA	Sertraline, Amit	NA	Dec
43 CR	27 M	SLE	Acute	+	Eye Nose Oral	+	EM + - +	+[16,38,39]	+ + + -	MMF, HCTZ	IV MP	Rec

Abbreviations: -, negative; +; positive; Abx, antibiotic medications otherwise unspecified; A/C, amoxicillin and clavulanic acid; Acute, acute onset of lesions < seven days; ACLE; acute cutaneous lupus erythematosus; Acr, acral involvement; Amit, amitriptyline; Amp-gent, ampicillin and gentamicin; ANA, antinuclear antibody; Analgscs, analgesic medications otherwise unspecified; Azat, azathioprine; Brdr, borderline; Bx, biopsy findings; Ca, case; Carb, carbamazepine, C/C, cloxacillin and ceftriaxone; Chlordiazepoxde, chlordiazepoxide; Chlor, chloroquine; CR, current report; Cyclo, cyclophosphamide; Dec, deceased; Dexa, dexamethasone; DIF, direct immunofluorescence; DsD; anti-double stranded DNA antibody; Dx, diagnosis; EM, pathology consistent with erythema multiforme; Erythromy, erythromycin; Gen, genital; Hc, hydrocortisone; HCTZ, hydrochlorothiazide, Hydrox, hydroxychloroquine; I, initial presentation of lupus; IV, intravenous; IVIg, intravenous immunoglobulin; La, anti-La/SSB antibody; LI, lymphocytic infiltrate; M, man; Mcn, mucin; Meds, medications; MMF, mycophenolate mofetil; MP, methylprednisolone; ; Mtx, methotrexate; Muc, mucosa; NA, not available or test not performed; Oc, outcome; Photo, photodistribution or photoaccentuation on presentation initially at least initially; Plasma, plasmapheresis; Pred, prednisone; Predn; prednisolone; Rec, recovered; Ref, reference; Ro, anti-Ro/SSA antibody; Ser, serologic findings; SCLE, subacute cutaneous lupus erythematosus; SLE, systemic lupus erythematosus; Sub, subacute onset of lesions (defined as two to four weeks); Sulfa, Sulfasalazine; TEN, histologic findings consistent with toxic epidermal necrolysis; Trastzmb, trastuzumab; VI, vacuolar interface; Vlva, vulva; W, woman

1 Both acute cutaneous lupus erythematosus (ACLE) and subacute cutaneous lupus erythematosus-like toxic epidermal necrolysis (SCLE-like TEN) are included in this review, as both resembled TEN both histologically and clinically. Cases cited in literature as SCLE-like TEN based on clinical appearance of rash are categorized as SLE in column three if they meet criteria for by either American College of Rheumatology (ACR) or Systemic Lupus International Collaborating Clinics (SLICC).

2 The following cases are excluded from this review: Horne et al [47] due to insufficient clinical information, Despain et al. [48] since biopsy did not show erythema multiforme (EM) or TEN, and cases in which biopsies at time of TEN-like rash were not performed [49-51].

3 This column lists the case number in our review ordered by age and the respective journal reference [bracketed].

4 The presence or absence of systemic, subacute or acute cutaneous lupus in the associated case is noted. (I) is used to designate initial presentation if the former diagnosis was made at the time of the evolving TEN-like ACLE eruption.

5 Onset refers to whether the TEN-like ACLE evolved in an acute (less than seven days to full extent of blistering eruption) or subacute (greater than 14 days) manner.

6 This column references whether or not the TEN-like ACLE eruption first presented in a photodistributed location.

7 Muc documents presence or absence of mucous membrane involvement with TEN-like ACLE. Conjunctival injection is interpreted as positive involvement. Oral involvement connotes anywhere in the oral cavity, including buccal mucosa, tongue, and gingiva.

8 Acral involvement noted in this column specifically refers to involvement of the hands and or feet with TEN-like ACLE eruption.

9 The presence or absence of background pathologic features of lupus, including vacuolar interface dermatitis at the periphery of the EM or TEN-like changes, mucin, and a mild to moderate lymphocytic infiltrate are listed. A sparse or minimal infiltrate is designated negative.

10 The results of direct immunofluorescence (DIF), if available, are reported. Results are designated positive if a pattern supportive of cutaneous lupus is noted: this includes positive fluorescence of immunoglobulin and/or complement at the basement membrane zone/ dermal epidermal junction/epidermal basal layer basal keratinocytes. If the reference distinguished the basement membrane zone and dermal epidermal junction in terms of deposition, this distinction is mentioned in a footnote.

11 This column lists the results of the following serologic studies-anti-nuclear antibody, double stranded DNA, Sjogren syndrome A (Ro) antibody, and Sjogren syndrome B (La) antibody.

12 This column references whether or not patient exposure to medications preceded the TEN-like ACLE eruption.

13 Treatment used for the TEN-like ACLE eruption is referenced in this column.

14 This column documents whether the patient recovered or expired as a consequence of the TEN-like ACLE eruption.

15 IgM, IgG, C3 and IgA is present at the basement membrane zone.

16 A granular pattern of immunofluorescence is present.

17 The specific pattern of immunofluorescence staining, that is granular or linear, is not provided.

18 C3 is deposited in dermal blood vessels.

19 One of multiple biopsies showed full thickness epidermal necrosis that the authors discounted as secondary to longstanding separation of epidermis. However, this fits our current review criteria for TEN-like ACLE, that is a biopsy demonstrating EM or TEN-like necrosis. Background features of lupus are also present.

20 This report distinguishes that IgG was deposited at the BMZ and that IgA, C3, and fibrin were found along the dermoepidermal junctional (DEJ).

21 IgG is present in epidermal keratinocytes.

22 Perivascular IgM is present.

23 This report mentions that all medications were stopped but did not state specifically which medications the patient was taking.

24 This patient did not respond to treatment until plasma exchange was initiated.

25 This report specifically notes the IgG to be moderate and the IgA and C3 to be faint.

26 IgG, IgM, C3, and faint IgA are present both in the epidermal basal layer and in suprabasal keratinocytes.

27 Granular C3 is demonstrated on the blister roof, along with a linear fibrin band.

28 IgG, IgM and C3 are present along the basement membrane zone (BMZ).

29 IgG is deposited along the BMZ.

30 Three plus IgM and one plus IgG3 are present along the BMZ.

31 Discontinuous C3 and fibrinogen along BMZ are documented.

32 C3, IgM, and IgG are present along dermal blood vessels.

33 This patient did not respond to treatment until dapsone was initiated.

34 C3, IgM, and IgG are noted to extend around appendages.

35 IgG and C3 along BMZ are present.

36 This report only notes that cytoid bodies (IgG, IgA, and C3) were found.

37 IgG deposition is noted to be focal.

38 IgM, C3, and C5-9 are present along the DEJ.

39 The presence of fine IgG is noted both in epidermal keratinocytes and along the epidermal BMZ.