Toxic Epidermal Necrolysis-Like Cutaneous Lupus in Pediatric Patients: A Case Series and Review

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abstract

Bullous eruptions in patients with underlying systemic lupus erythematosus (LE) can mimic toxic-epidermal necrolysis (TEN), a rapidly progressive mucocutaneous reaction usually associated with medication use. Differentiating between classic drug-induced TEN and TEN-like cutaneous LE is important but difficult. We report a series of 3 patients with pediatric systemic LE who were admitted with severe worsening of skin disease resembling TEN. However, the initial photo-distribution of the eruption, subacute progression, limited mucosal involvement, mild systemic symptoms, supportive biopsy and laboratory results, and lack of culprit drugs was more suggestive of a TEN-like cutaneous LE. These patients recovered with various systemic immunosuppressive medications including methylprednisolone, intravenous immunoglobulin, and plasmapheresis. Our cases are rare and demonstrate key clinical and histologic features of TEN-like cutaneous LE in young patients and the importance of differentiating this entity from drug-induced TEN.

Diagnosing bullous eruptions in pediatric patients with systemic lupus erythematosus (SLE) is difficult as the differential diagnosis is broad and includes drug reactions such as toxic-epidermal necrolysis (TEN)/Stevens-Johnson syndrome (SJS), bullous SLE, Rowell syndrome, and TEN-like cutaneous lupus erythematosus (LE).

TEN/SJS are severe idiosyncratic reactions characterized by extensive mucocutaneous necrosis with blistering and systemic symptoms. TEN-like cutaneous LE has been reported in the setting of systemic lupus flares though very few cases have been reported in children.

We report 3 cases of TEN-like cutaneous LE in patients with pediatric SLE. Though they were initially thought to have drug-induced TEN/SJS, they were ultimately diagnosed with TEN-like cutaneous LE, highlighting the importance of recognizing this rare entity.

CASE 1

A 15-year-old white girl was admitted for a 1-month history of progressive rash and fever. She was diagnosed 9 months earlier with SLE, manifested by malar rash, positive antinuclear antibody (ANA), positive anti-double stranded DNA (dsDNA) antibody, and mild leukopenia and anemia, for which she had been treated with hydroxychloroquine and prednisone. She improved with this treatment and had been weaned to 5 mg of prednisone. One month before admission, she developed a photodistributed rash on the face, upper trunk, and extremities, and hydroxychloroquine was discontinued because of concerns for a drug reaction. She was seen 1 week later for worsening rash and fever. On examination, she was febrile, with diffuse, pruritic, violaceous papules and plaques on the face, upper trunk, and extremities. Mucosal involvement was limited to the lips and oral mucosa. A biopsy was performed and showed subepidermal blisters and interface dermatitis, consistent with TEN-like cutaneous LE (Figures 1A and 1B). She was treated with methylprednisolone, intravenous immunoglobulin, and plasmapheresis over the next several days. She was able to taper off prednisone with no skin disease recurrence. She was subsequently discharged with a low dose of prednisone.

reaction. Hydroxychloroquine was restarted 4 days before admission as her rash was thought to be most consistent with a cutaneous LE flare. On the day of admission, she had acute worsening of cutaneous lesions, bullae, and fever.

Physical examination revealed pink papules and annular plaques with overlying erosions and vesiculation distributed on photoexposed skin (Fig 1A and B). Conjunctival hyperemia and fibrinous exudates on the lips and hard palate were noted. External genital examination was normal. Laboratory tests were significant for leukocytosis with neutrophil predominance, transaminitis, increasing anti-dsDNA antibody, and decreasing complement proteins 3 (C3) and 4. Due to concerns for drug reaction, medications including hydroxychloroquine were discontinued. Skin biopsy revealed interface dermatitis involving the dermal appendages and individually necrotic keratinocytes (Fig 2A). Direct immunofluorescence (DIF) was positive for lupus band, demonstrating granular staining of the basement membrane with immunoglobulin (Ig) M, IgG, C3, and IgA (Fig 2B). Because this can also be seen in bullous LE, enzyme-linked immunosorbent assay was performed for circulating collagen VII antibodies, and was negative.

Despite treatment with methylprednisolone and dapsone, the patient continued to have extension of the rash to the buttocks, thighs, and back (Fig 1C). Repeat biopsy revealed extensive epidermal necrosis that can be seen with TEN/SJS or TEN-like cutaneous LE (Fig 2C). The patient was given intravenous immunoglobulin G (IVIG) 3 g/kg over 3 days and started on mycophenolate mofetil. Dapsone was discontinued. Our patient slowly improved and was discharged on prednisone and mycophenolate mofetil. One year after hospitalization, hydroxychloroquine was resumed without incident.

**CASE 2**

An 11-year-old Asian girl was admitted with worsening skin eruption over the preceding month. She had a 4-month history of SLE with positive ANA, positive anti-Smith antibody, positive antiribonucleoprotein antibody, hypocomplementemia, acute cutaneous lupus, oral ulcers, and class III lupus nephritis. Prednisone and hydroxychloroquine were started 4 months before admission and mycophenolate mofetil was started 1 month prior.

On admission, she had confluent, bright pink, scaly, annular plaques
on sun-exposed areas of the head, neck, upper trunk, and arms. Erosions were present on the neck, back, shoulders, lips, and vulva. Her laboratory studies revealed transaminitis, increasing anti-dsDNA antibody, and decreasing C3 and complement protein 4. Due to concerns for possible drug reaction, hydroxychloroquine and mycophenolate mofetil were discontinued.

Despite high-dose methylprednisolone, she continued

### TABLE 1 Summary of Cases of SJS/TEN-like LE in Pediatric Patients

<table>
<thead>
<tr>
<th>Author</th>
<th>Age, y/ Gender</th>
<th>Photo-distribution</th>
<th>Mucous Membrane Involvement</th>
<th>Previous LE Diagnosis</th>
<th>Pertinent Laboratory Abnormalities</th>
<th>Histology</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yu</td>
<td>15/girl</td>
<td>Yes</td>
<td>Lips</td>
<td>Yes</td>
<td>ANA 1:1280, increasing anti-dsDNA, decreasing complement levels, anemia</td>
<td>Extensive epidermal necrosis and subepidermal clefting, interface dermatitis around pilosebaceous unit</td>
<td>Systemic steroids, intravenous IgG, mycophenolate mofetil, dapsone</td>
</tr>
<tr>
<td>Yu</td>
<td>11/girl</td>
<td>Yes</td>
<td>Lips, ocular, vaginal</td>
<td>Yes</td>
<td>ANA 1:1280, anti-RNP positive, anti-Smith positive, increasing anti-dsDNA, decreasing complement levels, anemia, transaminitis</td>
<td>Not available</td>
<td>Systemic steroids, intravenous IgG, plasmapheresis</td>
</tr>
<tr>
<td>Yu</td>
<td>18/boy</td>
<td>Yes</td>
<td>Lips</td>
<td>Yes</td>
<td>Increasing anti-dsDNA, decreasing complement levels, anemia, thrombocytopenia, transaminisits, elevated amylase and lipase</td>
<td>Extensive epidermal necrosis with sparse perivascular and interface lymphocytic dermatitis</td>
<td>Systemic steroids, mycophenolate mofetil</td>
</tr>
<tr>
<td>Lee et al²</td>
<td>12/girl</td>
<td>Yes</td>
<td>Oral, lips, ocular</td>
<td>No</td>
<td>ANA &gt;1:800, anti-dsDNA positive (trend unknown), anti-Smith positive, anti-Ro/SSA positive, anti-La/SSB positive, anti-RNP positive, hypocomplementemia (trend unknown), leukopenia, thrombocytopenia</td>
<td>Basal vacuolization with necrotic keratinocytes with perivascular lymphocytic infiltrate</td>
<td>Systemic steroids and hydroxychloroquine</td>
</tr>
<tr>
<td>Jang et al³</td>
<td>16/girl</td>
<td>Yes</td>
<td>Lips</td>
<td>No</td>
<td>ANA 1:640, anti-dsDNA positive (trend unknown), anti-Ro/SSA positive, anti-Smith positive, hypocomplementemia (trend unknown), leukopenia, anemia</td>
<td>Subepidermal clefting with interface dermatitis and marked necrosis of suprabasal keratinocytes</td>
<td>Systemic steroids, topical steroids and hydroxychloroquine</td>
</tr>
</tbody>
</table>
TABLE 2 Diagnostic Features of the Differential for Epidermal Necrosis in SLE

<table>
<thead>
<tr>
<th>Clinical</th>
<th>TEN</th>
<th>SJ/TEN-like Cutaneous LE</th>
<th>Bullous LE</th>
<th>Rowell Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flu-like prodrome; Dusky macules that coalesce, Bullae and sloughing of epidermis</td>
<td>May have preceding diagnosis of lupus; Bullae and sloughing of epidermis</td>
<td>Tense vesicles and bullae on sun-exposed areas</td>
<td>Features of DLE; Targetoid macules with centripetal spreading</td>
<td></td>
</tr>
<tr>
<td>Nikolsky sign</td>
<td>Positive</td>
<td>Positive or negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Mucous membrane involvement</td>
<td>Severe</td>
<td>Less severe and predominantly oral mucosa</td>
<td>Sometimes</td>
<td>Sometimes</td>
</tr>
<tr>
<td>Serology (ANA, anti-dsDNA, anti-Ro/La, RF)</td>
<td>Negative</td>
<td>ANA positive, Anti-dsDNA positive (often); Anti-Ro/SSA or La/SSB positive (often); RF negative</td>
<td>ANA positive, RF negative</td>
<td>ANA positive (speckled); Anti-Ro/SSA or La/SSB positive; RF positive</td>
</tr>
<tr>
<td>Histopathology</td>
<td>Full thickness epidermal necrosis with sparse superficial lymphocytic inflammatory infiltrate</td>
<td>Full thickness epidermal necrosis with sparse superficial lymphocytic inflammatory infiltrate; Features of interface dermatitis</td>
<td>Vacuolar degeneration of basal layer resulting in subepidermal blister with predominantly neutrophilic infiltrate</td>
<td>Necrotic keratinocytes with subepidermal blistering and a sparse lymphocytic infiltrate consistent with erythema multiforme</td>
</tr>
<tr>
<td>IF</td>
<td>Negative</td>
<td>Direct: May show granular IgM, IgG, and/or C3 binding at the BMZ (lupus band); Indirect: Negative</td>
<td>Direct: Linear or granular IgG, C3, IgM, and IgA binding at BMZ; Indirect: Collagen VII antibodies binding on the dermal side of the BMZ</td>
<td>Negative</td>
</tr>
<tr>
<td>Drug etiology</td>
<td>Most cases</td>
<td>No</td>
<td>Some cases</td>
<td>No</td>
</tr>
<tr>
<td>Course</td>
<td>Evolves over 3–5 d and heals over 3–4 wk; Scarring may occur; Mortality up to 30%–40%</td>
<td>Subacute course with rapid improvement within 1–2 wk after treatment</td>
<td>Rapid response to dapsone treatment with cessation of blister formation within 1–2 d; May have intermittent exacerbations</td>
<td>May recur over many years</td>
</tr>
</tbody>
</table>


having fevers, and she developed bilateral eye drainage, photophobia, and increased skin involvement and tenderness. IVIG 3 g/kg (total) was given but she continued to worsen. She developed *Staphylococcus aureus* infection of the eyes and skin, for which she was treated with appropriate antimicrobial agents.

Given the TEN-like features, a diagnosis of TEN-like cutaneous LE was rendered. Plasmapheresis was started, and she steadily improved with reepithelialization of denuded epidermis. She was restarted on hydroxychloroquine 1 year later without recurrence of the TEN-like cutaneous LE.

**CASE 3**

An 18-year-old Asian man with a 2-year history of SLE manifested by discoid lupus erythematosus (DLE), lupus nephritis, lupus cerebritis, and Coombs-positive hemolytic anemia, and myocarditis was admitted for fever, malaise, myalgias, and worsening diffuse rash. This occurred 2 weeks after receiving clindamycin for wisdom teeth extraction. The rash started on the face and progressed to the trunk and extremities. Physical examination revealed hemorrhagic erosions and crusting on the lips, soft palate, scalp, and face, with trace injection of conjunctiva. Violaceous papules and plaques with flaccid vesicles were seen on the trunk and extremities without involvement of the genital mucosa. Laboratory testing was significant for decreasing C3, increasing anti-dsDNA antibody, mild leukopenia, anemia, transaminitis, elevated creatine kinase, and elevated amylase and lipase.

Skin biopsies demonstrated subepidermal blister with full thickness epidermal necrosis and interface dermatitis most consistent with TEN-like cutaneous LE. Methylprednisolone and mycophenolate mofetil were administered with substantial systemic and cutaneous improvement and normalization of laboratory values. He was discharged on oral clindamycin for *S aureus* skin infection without subsequent flare in the skin eruption.

Four months after discharge, he was admitted again with diffuse erythematous plaques with central erosions and hemorrhagic crusting, milder but similar to previous flare. There were no recent changes in his medications to suggest a drug reaction. Interestingly, before the initial SLE diagnosis, he reportedly had a similar mucocutaneous eruption that was initially diagnosed as SJS. As his course evolved, he was ultimately diagnosed with SLE.
Adnexal involvement Periadnexal lymphocytic infiltrate, sparse, superficial lymphocytic infiltrate

Minor Criteria (Must Fulfill at Least 1)
1. Absence of infectious or pharmacologic triggers
2. Absence of typical EM locations (acral and mucosal)
3. Presence of at least 1 American Rheumatism Association criterion for diagnosis of SLE besides discoid rash and ANA and excluding photosensitivity, malar rash, and oral ulcers


REvised Diagnostic Criteria for Rowell Syndrome

Major Criteria (Must Fulfill All)
1. Presence of CCLE (SLE or chilblain lupus)
2. Presence of EM-like lesions (typical or atypical)
3. At least 1 positivity among speckled ANA, anti-Ro(SSA), and anti-La(SSB) antibodies
4. Negative DIF on EM-like lesions

Minor Criteria (Must Fulfill at Least 1)
1. Absence of infectious or pharmacologic triggers
2. Absence of typical EM locations (acral and mucosal)
3. Presence of at least 1 American Rheumatism Association criterion for diagnosis of SLE besides discoid rash and ANA and excluding photosensitivity, malar rash, and oral ulcers

DISCUSSION AND REVIEW OF THE LITERATURE

TEN-like cutaneous LE in pediatric SLE is rare. We have described 3 additional cases similar to others previously reported (Table 1). This form of cutaneous LE can be difficult to differentiate from the other blistering dermatoses occurring in the setting of SLE including TEN/SJS, bullous SLE, and Rowell syndrome (Table 2).

TEN/SJS is an acute vesiculobullous reaction characterized by rapidly progressive, painful mucocutaneous erosions, widespread flaccid bullae, epidermal necrosis, and prominent systemic symptoms. It is triggered by a medication in 80% to 95% of cases.1,5 Latency of drug exposure to onset of TEN/SJS is usually within 3 weeks, and sooner with previous exposure. TEN/SJS occurs at a higher frequency in patients with immune-altering diseases such as pediatric SLE (1%–2%).6,7 Bullous SLE8 and Rowell syndrome9,10 are rare manifestations of lupus, particularly in children. In previous reports, the terms bullous SLE and Rowell syndrome may have been used less specifically to describe any blistering dermatoses in SLE.9,11,12 More recently, Rowell syndrome diagnostic criteria have been revised to clarify Rowell syndrome from other variants of LE and erythema multiforme (Table 3).13

Similar to the 4 cases of TEN-like LE in adults presented by Ziemer et al,14 our cases demonstrated clinical features of LE that led us to this diagnosis. All of our patients had an existing diagnosis of SLE and all initially developed a photodistributed annular eruption resembling cutaneous LE, which progressed to diffuse epidermal necrosis subacutely over the course of weeks to months. Mild mucous membrane involvement was observed with mild lip erosions predominating, though case 2 also demonstrated conjunctivitis and genital erosions. The onset of worsening cutaneous eruption also coincided with decreasing complement levels and increasing anti-dsDNA antibodies, consistent with worsening SLE. All patients had mild fevers, myalgias, and malaise. Cases 1 and 2 had mild transaminitis; case 3 had significant transaminitis. Overall, the degree of systemic involvement is milder than in drug-induced TEN.

Our cases also demonstrated histopathologic features of LE, which can be helpful in differentiating from TEN/SJS (Table 4). Interface dermatitis present on an early biopsy in case 1 and in case 3 helped with the diagnosis of cutaneous LE. Later biopsies in cases 1 and 3 were less helpful, demonstrating full thickness epidermal necrosis characteristic of TEN/SJS.

Though a drug reaction was considered in all cases and nonessential drugs were discontinued, rechallenge with the potential etiologic drugs did not elicit a repeat reaction, as would be expected in TEN/SJS. There are reports of hydroxychloroquine-induced TEN,15,16 which was a concern in cases 1 and 2 leading to its initial discontinuation, although both patients have had subsequent reintroduction of hydroxychloroquine without incident. Differentiating drug-induced TEN/SJS in patients with LE from TEN-like cutaneous LE may be difficult, and it is possible that some previously reported cases may have been misclassified.14,17–19

Of the cases we included here and reviewed from the literature, no patients died as a result of his or her...
illness compared with a mortality rate of 7.5% reported in pediatric TEN. In a series of 4 adult patients with TEN-like cutaneous lupus, 2 died of their disease, whereas neither of the 2 previously reported pediatric cases were fatal. Although the small number of reported patients limits conclusions, it may be that pediatric patients with TEN-like cutaneous LE have a lower mortality compared with children with drug-induced TEN/SJS. Therapy for TEN-like cutaneous LE eruption has not been well studied. In the cases reviewed, parenteral corticosteroids, IVIG, and plasmapheresis were effective. We describe 3 pediatric cases of TEN-like cutaneous LE associated with SLE. The paucity of significant systemic symptoms, lack of recurrence with drug rechallenge, and underlying flaring SLE distinguishes these cases of TEN-like cutaneous LE from drug-induced TEN/SJS. Prompt recognition with early biopsy of lesions in TEN-like cutaneous LE is important to prevent inappropriate diagnosis of drug allergy and allow early institution of appropriate treatment.

REFERENCES


ABBREVIATIONS

ANA: antinuclear antibody
C3: complement protein 3
DIF: direct immunofluorescence
DLE: discoid lupus erythematosus
dsDNA: double stranded DNA
Ig: immunoglobulin
IVIG: intravenous immunoglobulin G
LE: lupus erythematosus
SJS: Stevens-Johnson syndrome
SLE: systemic lupus erythematosus
TEN: toxic-epidermal necrolysis
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