Acute vesiculobullous eruption in lupus patient on trimethoprim-sulfamethoxazole

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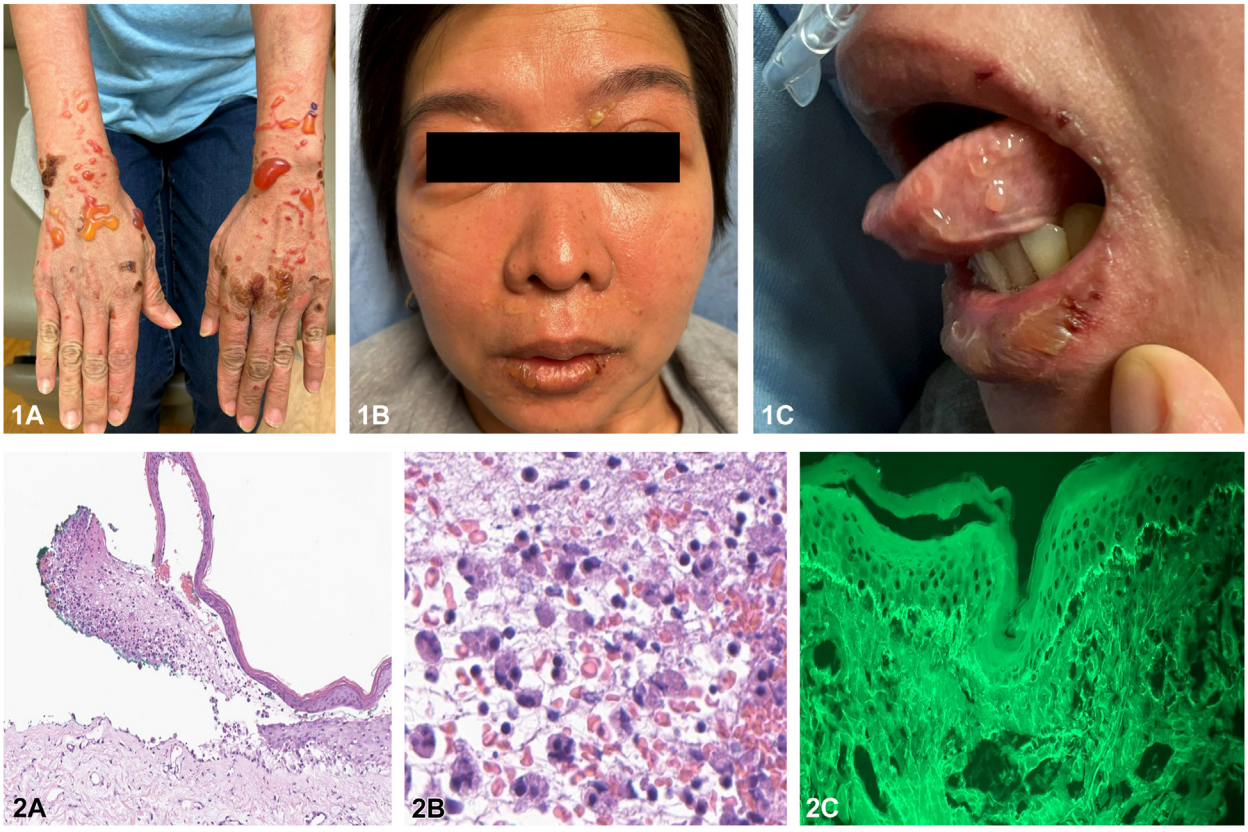

CLINICAL CASE

A 48-year-old woman with systemic lupus erythematosus and class IV lupus nephritis treated with hydroxychloroquine 200 mg/day and prednisone 20 mg/day starting 1 month earlier presented with a new, acute-onset vesiculobullous eruption. This vesiculobullous eruption started two weeks after initiating trimethoprim-sulfamethoxazole (TMP-SMX) for *Pneumocystis jirovecii* pneumonia prophylaxis. She described the eruption as burning and painful.

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Examination revealed erythema with overlying tense, straw-colored bullae on the dorsal distal upper extremities, periocular skin, vermillion lips, and lateral tongue (Fig 1). Periorbital edema and conjunctival injection were noted. Both Nikolsky and Absoe-Hansen signs were negative.

Question 1: What is the most likely diagnosis?

A. Bullous pemphigoid (BP)

B. Bullous systemic lupus erythematosus

C. Erythema multiforme

D. Pemphigus vulgaris

E. Stevens-Johnson Syndrome

Answers:

A. BP — Incorrect. While BP can present with tense straw-colored bullae and negative Nikolsky sign, BP typically occurs in elderly patients with a medication history notable for dipeptidyl peptidase 4 inhibitors (sitagliptin), PD-1 inhibitors (nivolumab, pembrolizumab), loop diuretics (furosemide), and penicillin-type antibiotics.

B. Bullous systemic lupus erythematosus — Correct. Bullous systemic lupus erythematosus (SLE) is the most likely diagnosis in a patient with a history of SLE and the above clinical presentation. Bullous SLE is a rare cutaneous manifestation of SLE that presents with tense, straw-colored bullae.[1] Intraoral blisters erosions and blistering along the vermillion lip are often observed.

C. Erythema multiforme — Incorrect. While the distribution of lesions on acral and oral mucosal sites is characteristic of erythema multiforme, the morphology of the lesions shown in Fig 1 is not consistent with the targetoid appearance of erythema multiforme.

D. Pemphigus vulgaris — Incorrect. Pemphigus vulgaris presents with flaccid bullae and a positive Nikolsky sign due to acantholysis.

E. Stevens-Johnson Syndrome — Incorrect. Although Stevens-Johnson syndrome is commonly associated with preceding TMP-SMX use, clinical findings typically include severe mucous membrane involvement, dusky patches and flaccid bullae, large erosions, and positive Nikolsky sign.

Question 2: Which histopathologic and direct immunofluorescence (DIF) findings are classically observed in this condition?

A. Subepidermal blister with a predominantly neutrophilic infiltrate; positive DIF for IgG, C3, IgA, IgM in a granular pattern along the basement membrane zone (BMZ).

B. Intraepidermal vesicles with acantholysis; positive DIF for intercellular IgG.

C. Full-thickness epidermal necrosis; negative DIF.

D. Subepidermal blister with eosinophils; positive DIF for IgG and C3 in a linear pattern along the BMZ.

E. Interface dermatitis with vacuolar alteration of the basal layer; positive DIF for IgM in a granular pattern at the dermoepidermal junction.

Answers:

A. Subepidermal blister with a predominantly neutrophilic infiltrate; positive DIF for IgG, C3, IgA, IgM in a granular pattern along the BMZ — Correct. Bullous SLE is characterized by subepidermal blister formation with a predominantly neutrophilic infiltrate (Fig 2, *A* and *B*), and DIF in bullous SLE classically demonstrates deposition of IgG, IgM, IgA, and C3 ("full house") along the BMZ in a granular, linear, or mixed pattern (Fig 2, *C*).[2] IgG may demonstrate *in vivo* antinuclear antibody. The target antigen is collagen VII.

B. Intraepidermal vesicles with acantholysis; positive DIF for intercellular IgG — Incorrect. Intraepidermal blister with acantholysis and intercellular IgG is characteristic of pemphigus. In mucocutaneous pemphigus vulgaris, the target antigens are desmoglein 3 and desmoglein 1.

C. Full-thickness epidermal necrosis; negative DIF — Incorrect. Full-thickness epidermal necrosis and necrotic keratinocytes are observed in Stevens-Johnson syndrome/toxic epidermal necrolysis. Stevens-Johnson syndrome/toxic epidermal necrolysis typically occurs within 7—21 days following causative drug ingestion.

D. Subepidermal blister with eosinophils; positive DIF for IgG and C3 in a linear pattern along the BMZ — Incorrect. A subepidermal blister with eosinophils and linear IgG and C3 at the BMZ suggests BP, in contrast to the subepidermal neutrophils and granular immunofluorescence observed in bullous SLE. The target antigens in BP are BPAG1 and BPAG2 (collagen XVII). Most cases

of drug-induced BP occur within 3 months following drug administration, but a delayed onset of 1 year or longer is associated with dipeptidyl peptidase 4 and PD-1 inhibitors.

E. Interface dermatitis with vacuolar alteration of the basal layer; positive DIF for IgM in a granular pattern at the dermoepidermal junction — Incorrect. Interface dermatitis with vacuolar alteration is more characteristic of acute or subacute cutaneous lupus erythematosus rather than bullous SLE. Drug-induced subacute cutaneous lupus erythematosus occurs following a variable latency ranging from weeks to months.

Question 3: Which of the following is the most appropriate next step in the management of this patient?

A. Administer rituximab

B. Increase prednisone dose

C. Initiate dapsone

D. Resume TMP-SMX

E. Start intravenous immunoglobulin (IVIg)

Answers:

A. Administer rituximab — Incorrect. Rituximab can be effective in SLE and bullous SLE, but should follow the first-line treatment (dapsone) due to cost and immunosuppression.

B. Increase prednisone dose — Incorrect. High-dose prednisone is also effective for bullous SLE, but is not the first-line treatment, and long-term administration is associated with infections and osteoporosis.

C. Initiate dapsone — Correct. Dapsone effectively treats bullous SLE by targeting neutrophil chemotaxis and respiratory burst. Additionally, dapsone serves as a second-line alternative for *Pneumocystis jirovecii* pneumonia prophylaxis. Prior to starting dapsone, glucose-6-phosphate dehydrogenase should be evaluated, and complete blood count and liver function tests should be monitored after treatment initiation.

D. Resume TMP-SMX — Incorrect. Unlike dapsone, TMP-SMX is associated with phototoxicity and does not serve as an effective treatment for bullous SLE.[3]

E. Start IVIg — Incorrect. IVIg is an option for severe or refractory bullous SLE. The associated high cost and limited access make IVIg a third or fourth-line treatment option.

Abbreviations used:

BMZ: basement membrane zone
BP: bullous pemphigoid
DIF: direct immunofluorescence
IVIg: intravenous immunoglobulin
SLE: systemic lupus erythematosus
TMP-SMX: trimethoprim-sulfamethoxazole

Key words

autoimmune blistering disease; direct immunofluorescence; immunobullous; lupus erythematosus; trimethoprim-sulfamethoxazole

Conflicts of interest

None disclosed.

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