

## 21-Year-Old Woman With a Painful Rash



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**A** 21-year-old black female with past medical history of deep vein thrombosis and anaphylaxis presented as a hospital transfer for a progressive vesicular rash. Three weeks before admission, she developed a midline facial pruritic, burning rash and arthralgias. She was pregnant during the initial rash eruption; however, she experienced a first trimester miscarriage and upper extremity deep venous thrombosis 1 week after rash eruption. At the time of admission to our hospital, her rash had progressed to involve the axillae, neck, trunk, arms, head, and oral and genital mucosa.

Her medications upon transfer included Solu-Medrol 60 mg intravenously twice a day, hydromorphone and fentanyl for pain control, and enoxaparin. She had no significant family history of skin conditions.

On physical exam, vitals included a blood pressure of 131/90 mm Hg, pulse of 55 beats/min, respiratory rate of 13 breaths/min, and temperature of 36.9°C. Her body mass index was 32.8 kg/m<sup>2</sup>. Cardiac exam revealed regular rhythm with no rubs or gallops. Lungs were clear to auscultation bilaterally. Abdomen was soft and nontender to palpation. No lymphadenopathy on exam. There was synovitis in joints of hands. Eyes demonstrated some clear discharge bilaterally. Skin exam demonstrated areas of well-demarcated hypopigmented erosions as well as discrete and coalescing tense bullae and vesicles on erythematous along with normal surfaces. Her rash involved the skin on axillae, neck, trunk, arms, head, and the oral and genital mucosa.

Initial laboratory testing revealed the following (reference ranges provided parenthetically): white blood cell count of  $20.8 \times 10^9$  L (3.4 to  $9.6 \times 10^9$  L),

hemoglobin of 9.1 g/dL (12.0 to 15.05 g/dL), mean corpuscle volume of 83.6 fL (78.2 to 97.9 fL), platelet count of  $127 \times 10^9$  L (157 to  $371 \times 10^9$  L) and normal renal function with no protein on urinalysis.

### 1. Which of the following is the most likely explanation for this patient's rash?

- Autoimmune
- Viral infection
- Allergic reaction
- Pregnancy associated
- Idiopathic

Given her age, arthralgias, recent deep vein thrombosis, and miscarriage, an autoimmune condition is the most likely etiology for this patient's rash. A viral infection associated with rashes such as disseminated herpes simplex virus, hepatitis C, or disseminated herpes zoster could be a possibility; however, these viruses are not associated with deep venous thromboses and miscarriages. Given the time course and lack of new medications or exposures, an allergic reaction is less likely the etiology of this patient's rash. A bullous rash can be associated with pregnancy such as pemphigus gestationis; however, presence of extracutaneous symptoms, such as synovitis, would not be present in pregnancy-related rashes.<sup>1</sup> A presumption that the cause is idiopathic as the final diagnosis would be premature without a full evaluation. Importantly, in older patients presenting with a bullous rash, malignancy would need to be excluded, such as Waldenström macroglobulinemia.

Our patient underwent significant autoimmune and infectious evaluation at both an outside institution and again at our hospital to determine the etiology of the patient's symptoms.

**See end of article for correct answers to questions.**

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2. Which of the following is the next best step to perform in this patient to secure the diagnosis?

- Anti-Smith antibody (anti-Sm) serologic testing
- Anti-double stranded DNA (anti-dsDNA) serologic testing
- Antinuclear antibody (ANA) serologic testing
- Anti-histone antibody serologic testing
- Skin biopsy

Anti-Smith antibody, anti-dsDNA, and ANA serologic testing can provide support if elevated for an autoimmune etiology, such as systemic lupus erythematosus, for the etiology of the rash; however, it does not secure the diagnosis. Anti-histone antibody testing is associated with drug-induced lupus. It can be helpful in the initial evaluation for this patient given new medication use; however, it would not secure the diagnosis. Although laboratory evaluation is necessary, including all of the above testing, skin biopsy would be the next best step in securing a diagnosis for this patient.

Laboratory studies revealed anti-dsDNA level of 320 IU/mL (<30.0 IU/mL), ANA greater than 12 U ( $\leq 1.0$  U is negative;  $\geq 6.0$  U is strongly positive), anti-Sm level of  $>8.0$  U ( $<1.0$  U is negative) and low C3 and C4 levels. Antinuclear antibody titer was 1:1280 with speckled pattern on immunofluorescence. Beta 2 GPI antibodies and anti-phospholipid antibodies were both negative. Herpes simplex virus (HSV) type 1 immunoglobulin G (IgG) antibody and HSV type 2 IgG antibody were positive. Hepatitis C serology was negative. Varicella zoster virus IgG antibody was positive. Indirect immunofluorescence demonstrated positive anti-basement membrane zone (anti-BMZ), monkey esophagus antibody, and human split skin antibody in a dermal pattern.

Skin biopsy demonstrated subepidermal blisters with brisk papillary dermal neutrophilic inflammation; direct immunofluorescence revealed IgG, IgM, and IgA linear deposition along the BMZ. Multiple swabs of lesions for HSV and varicella zoster virus polymerase chain reaction were negative.

3. Which one of the following is most likely to be the cause of this patient's rash?

- Pemphigus vulgaris (PV)
- Bullous pemphigoid (BP)
- Dermatitis herpetiformis (DH)
- Bullous systemic lupus erythematosus (BSLE)
- Disseminated herpes simplex virus

Autoimmune blistering skin diseases are pathologically divided into intraepidermal versus subepidermal lesions.<sup>2</sup> Intraepidermal lesions clinically present as flaccid (Nikolsky positive) mucocutaneous vesicles and bullae.<sup>2</sup> Subepidermal lesions clinically manifest as tense mucocutaneous bullae and vesicles.<sup>2</sup> Autoimmune intraepidermal blistering skin diseases include PV, pemphigus foliaceus, and IgA pemphigus.<sup>2</sup> Subepidermal autoimmune blistering diseases include BP, DH, and BSLE.<sup>2</sup>

Pemphigus vulgaris is more common in middle-aged Asian and Mediterranean females.<sup>3</sup> Clinically, patients present with a more indolent onset of flaccid bullae primarily starting on mucosal surfaces with progression to skin lesions over several months.<sup>4</sup> On biopsy, intraepidermal blisters are present.<sup>2,3</sup> This diagnosis is less likely in this patient given her age and tense bullae on exam.

Bullous pemphigoid is the most common autoimmune blistering disease.<sup>5</sup> Generally, it presents in patients over the age of 70 years.<sup>2,5</sup> Clinically, patients generally present with tense bullae on the abdomen and flexure surfaces of lower extremities.<sup>2,4,5</sup> On biopsy, there are subepidermal blisters with serology demonstrating antibodies to hemidesmosomes.<sup>2,4,5</sup> Bullous pemphigoid is less likely in this patient given her age and lack of lower extremity predominance of rash distribution.

Dermatitis herpetiformis presents as grouped, tense vesicles and bullae on extensor surfaces of limbs, elbows, knees, and the buttocks. It rarely involves oral mucosa.<sup>2,6</sup> It is closely associated with celiac disease and younger females. Biopsy demonstrates granular IgA deposits in the subepidermal region with neutrophilic

predominance.<sup>2,6</sup> Dermatitis herpetiformis is less likely in this patient given her extensive mucosal involvement, no history of gluten intolerance, and lack of exclusively IgA deposition on direct immunofluorescence.

Bullous systemic lupus erythematosus is most common in young females.<sup>4,7,8</sup> It presents with tense bullae and vesicles on mucocutaneous surfaces primarily along the axial body including the head, trunk, and neck, as well as the arms and hands.<sup>7,8</sup> On biopsy, there is subepidermal blistering. On immunofluorescence, immunoglobulin deposition is present at the BMZ.<sup>7-11</sup> Autoantibodies to collagen type VII are also present.<sup>7,8</sup> This patient fits the typical clinical picture of BSLE, being a young female with mucocutaneous tense bullae in a more axial distribution. This patient has antibody deposition at the BMZ which localize to the dermal side of salt-split skin, which are classic in BSLE making this the most likely diagnosis.<sup>7-10</sup>

Systemic HSV can present as a disseminated infection in pregnant patients if it is the first infection. Patients would generally present with fevers and painful vesicles that rupture and ulcerate over days rather than weeks, as in this patient. Skin swab would generally detect HSV DNA on polymerase chain reaction, which was not the case in this patient, showing that HSV is not the diagnosis.<sup>12</sup>

**4. Which one of the following statements about the diagnosis is most likely true in this patient?**

- The rash can only develop on erythematous skin
- The rash can only develop on sun-exposed areas
- It is more often found in darker-skinned women
- It is not associated with lupus nephritis
- It is associated with Epstein-Barr virus exposure

Bullous lesions can develop on both erythematous and normal skin. The bullous rash is not limited to sun-exposed areas of the skin.<sup>7,8</sup> Bullous systemic lupus

erythematosus is more prevalent in darker-skinned females making this the correct answer.<sup>7,8</sup> Bullous systemic lupus erythematosus is associated with arthralgias, cytopenias, lupus nephritis, and neuropsychiatric symptoms.<sup>7</sup> There is no correlation between BSLE and Epstein-Barr virus.

**5. What is the best choice for first-line treatment for this condition?**

- Dapsone
- Immunosuppression
- Rituximab
- Intravenous immunoglobulin (IVIG)
- Plasma exchange

Dapsone is the first-line treatment for BSLE with an efficacy of 90%.<sup>7</sup> Because of numerous side effects such as hepatitis, hemolytic anemia, and hypersensitivity reactions, it is often discontinued. Second-line therapies include immunosuppression, rituximab, IVIG, and plasma exchange.<sup>7,11</sup> Second-line treatments are determined based on provider preference and the presence of extracutaneous symptoms. Immunosuppression use such as cyclophosphamide, azathioprine, and mycophenolate mofetil demonstrate an efficacy of 70% in the improvement of BSLE and can be used in the presence of extracutaneous symptoms. The use of systemic corticosteroids as monotherapy demonstrate poor efficacy in rash control. Biologics such as rituximab, plasma exchange, and IVIG can be used; however, little data is available on efficacy as it is not frequently used.<sup>7,11</sup>

This patient was initially treated with high-dose oral steroids monotherapy at an outside institution with little improvement in symptoms. Upon transfer to our hospital, she was started on dapsone and mycophenolate mofetil. Despite therapy, the rash progressed. Plasma exchange sessions followed by rituximab infusions were initiated. Eventually, after several months of treatment, she had no further lesions. In the case of this patient, she required specialized wound care at a burn center given the extent of disease. Because of the refractory nature of disease requiring multiple lines of therapy, she had

a prolonged hospitalization of 2 months. As an outpatient, she continued to follow-up with the rheumatology department and was determined to have systemic lupus erythematosus; despite her initial presentation of BSLE being rare in an SLE patient. Fortunately, she obtained remission of all of her symptoms, but did have evidence of hypopigmentation, hyperpigmentation, and alopecia.

## DISCUSSION

Autoimmune blistering disorders are not a rare phenomenon. Bullous pemphigoid is the most common autoimmune blistering disorder with an incidence of up to 14 new cases per 1 million people annually.<sup>2</sup> Although BSLE is less prevalent, autoimmune bullous disorders require early detection and aggressive management due to the severity of disease including morbidity, mortality, and health care use if there is a delay in diagnosis.

Bullous systemic lupus erythematosus is a subepidermal autoimmune blistering disorder resulting in the development of tense bullae and vesicles. Bullous systemic lupus erythematosus is more prevalent in darker-skinned young females.<sup>7,8</sup> The clinical course is characterized by a progressive painful pruritic bullae and vesicles that develop on both erythematous and normal mucocutaneous surfaces. The rash can develop anywhere on the body but has a predominance for the axial skeletal region and is not worsened with light exposure.<sup>8</sup> Patients can have extracutaneous manifestations commonly seen in systemic lupus erythematosus such as arthralgias, cytopenias, neuropsychiatric lupus, serositis, and fevers. Lupus nephritis is also associated with half of all cases of BSLE.<sup>7,11</sup>

The initial evaluation for BSLE consists of laboratory serologic testing and tissue biopsy. Bullous systemic lupus erythematosus is commonly associated with an elevated ANA level, positive anti-dsDNA antibodies, and low complement levels. Sjogren syndrome-A (SS-A) and Sjogren syndrome-B (SS-B), anti-Sm, and anti-ribonucleoprotein (RNP) antibodies can also be elevated.

Tissue biopsy and indirect immunofluorescence is necessary to confirm the diagnosis. On biopsy there is evidence of subepidermal blistering. Direct and indirect immunofluorescence show antibody deposition at the BMZ which localize to the dermal side of salt-split skin which is characteristic for BSLE. There is also the presence of autoantibodies to collagen type VII, human split skin antibodies, and monkey esophagus antibodies.<sup>7,9,11</sup>

First-line treatment for BSLE is dapsone which has an efficacy of 90%. There is usually a cessation of new lesions within several days of therapy initiation.<sup>7,11</sup> Dapsone requires glucose-6-phosphate enzyme testing before initiation because of the risk of hemolytic anemia. Dapsone is often stopped because of the high side-effect profile including hepatitis and hypersensitivity reactions. In patients who cannot tolerate dapsone because of glucose-6-phosphate dehydrogenase deficiency or side effects, less-clear guidelines exist on second-line therapies. Second-line treatments include immunosuppression, oral corticosteroids, IVIG, plasma exchange, and biologics. As a second-line treatment if patients show no improvement in rash, systemic corticosteroids can be started as an adjunct; however, systemic corticosteroids demonstrate poor efficacy in rash control as monotherapy.<sup>7,11</sup> Patients with extracutaneous symptoms are often also started on immunosuppression with cyclophosphamide, mycophenolate mofetil, and azathioprine with significant improvement in symptoms. Intravenous immunoglobulin, plasmapheresis, and rituximab have also shown efficacy in the treatment of BSLE.<sup>7,11</sup> Besides medication treatment, patients with BSLE and other blistering skin disorders may need further management at a specialized burn center for wound care.

In general, blistering skin disorders require early diagnosis and aggressive treatment. Bullous systemic lupus erythematosus is not the most common cause of bullous autoimmune skin disorders; however, it is an entity that should remain on the differential given the severity of disease and

predominance of extracutaneous symptoms. It is particularly important to understand this entity because if a patient fails to respond to dapsone after several days of initiation, the disease can be difficult to treat and may require different forms of immunosuppression and specialized wound care.

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**CORRECT ANSWERS: 1. a. 2. e. 3. d. 4. c. 5. a.**