A Recalcitrant Case of Toxic Epidermal Necrolysis

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PRACTICE **POINTS**

- Toxic epidermal necrolysis can be difficult to diagnose and treat.
- Patients who are refractory to treatment should prompt further management considerations.

We describe a case that was initially diagnosed and treated as toxic epidermal necrolysis (TEN) by an outside hospital. After failure to improve on high-dose steroids and intravenous (IV) immunoglobulin, the patient was transferred to our hospital where he was subsequently diagnosed with a disseminated herpes simplex virus (HSV) infection. The patient recovered after 21 days of antiviral therapy. We review key physical examination findings that will help the clinician diagnose a viral etiology in the setting of an acute blistering eruption with mucosal involvement.

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One of the most severe complications of systemic medications is the development of a life-threatening rash, especially toxic epidermal necrolysis (TEN). Most patients can expect a full recovery if the complicating medication is discontinued early on in its course.[1] When suspected TEN does not improve despite discontinuation of the detrimental medication, other diseases must be considered, particularly immunobullous and infectious etiologies. Treatment of these diseases differs substantially; therefore, a quick diagnosis is crucial. We present a case of a patient with an acute blistering eruption that was initially diagnosed and managed as TEN but physical examination and histopathologic confirmed another diagnosis. We review key examination findings that can help differentiate the causes of an acute blistering eruption with mucosal involvement, allowing for earlier diagnosis and treatment of these patients.

Case Report

An 85-year-old immunocompetent man was admitted to an outside hospital with a pruritic blistering eruption associated with myalgia, weakness, and fatigue of 3 weeks' duration. The eruption initiated on the scalp and face and then spread down to the trunk and proximal arms and legs, with oral erosions also reported. An outside dermatologist was consulted on admission and performed a skin biopsy; the initial pathology was read as TEN. The patient was admitted to our institution on the same day, and all potentially complicating medications were stopped. He was treated with intravenous (IV) methylprednisolone sodium succinate 125 mg twice daily for 4 days and prednisone 40 mg daily for 9 days. With the rash worsening, the patient was restarted on methylprednisolone sodium succinate 40 mg every 8 hours approximately 3 weeks after admission, along with IV immunoglobulin at 2 g/kg over 3 days. When the patient did not respond to treatment, he was transferred to the University of California Irvine Medical Center for a higher level of care.

At that time, physical examination revealed numerous confluent erosions with honey-colored crust involving the entire face (Figure 1A) and sharp demarcation at the cutaneous lip (Figure 1B). There was a large erosion on the dorsal aspect of the tongue, but the rest of the oral mucosa was spared. The trunk and proximal extremities showed numerous grouped, punched-out erosions with scalloped borders (Figure 1C).

A repeat skin biopsy showed an ulcer with viral cytopathic changes. Immunoperoxidase studies demonstrated positive staining for herpes simplex virus (HSV) type 1 (Figure 2). The original slides were a frozen section from an outside facility and could not be obtained. A tissue culture and direct fluorescent antibody also confirmed HSV-1, and the patient was diagnosed with disseminated herpes. He was rapidly tapered off of the steroids and started on IV acyclovir 10 mg/kg every 8 hours for

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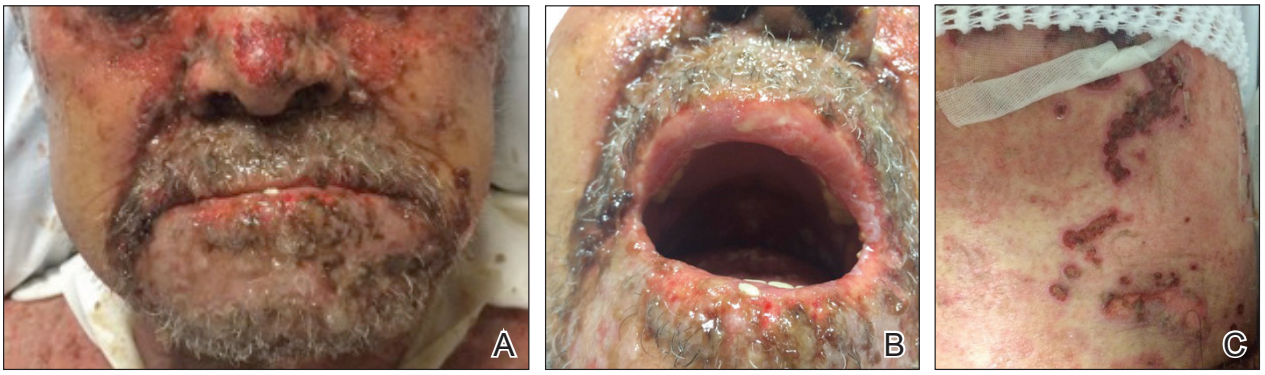

FIGURE 1. Numerous confluent erosions with honey-colored crust involving the face (A) and sharp demarcation of erosions at the cutaneous lip (B). There was a cluster of punched-out erosions with scalloped borders on the trunk (C).

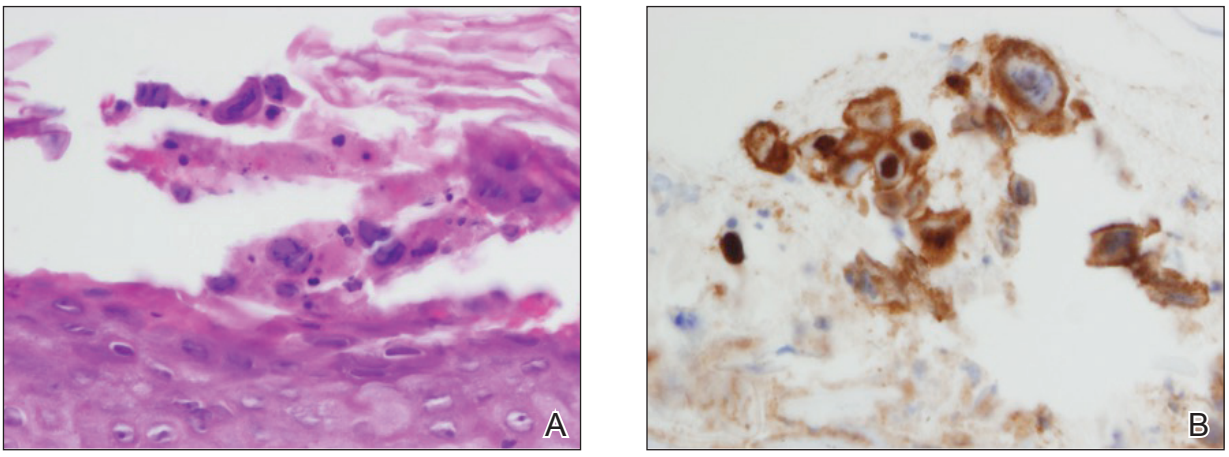

FIGURE 2. Multinucleated giant cells with nuclear molding and basophilic chromatin at the periphery of the nucleus (A)(H&E, original magnification ×400). Immunoperoxidase studies demonstrated positive staining for herpes simplex virus type 1 in lesional skin (B)(original magnification ×400).

21 days. All prior erosions reepithelialized within 7 days of treatment (Figure 3). The patient had an otherwise uncomplicated hospital course and was discharged on hospital day 21.

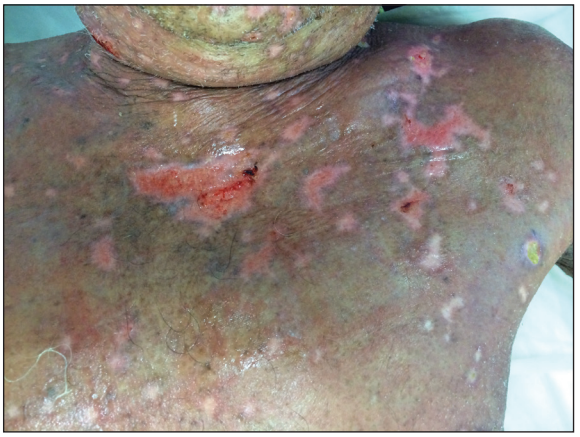

FIGURE 3. After treatment with acyclovir, the erosions reepithelialized within 7 days.

Comment

A patient with an acute generalized blistering eruption requires urgent workup and treatment given the potentially devastating sequelae. Toxic epidermal necrolysis and immunobullous diseases often are the first diagnoses to be ruled out. Certainly infections such as HSV can cause a vesicular and erosive eruption, especially in the setting of a poorly controlled dermatitis, but they typically are not in the same differential as the other diagnoses.

Clinical Presentation—This case highlights 2 key physical examination findings that can alert the clinician to a possible underlying herpetic infection. First, the distribution of this patient's oral lesions was telling. In most cases of TEN or pemphigus vulgaris, there is notable involvement of the oral mucosa, particularly the buccal and labial mucosa. Although herpes can involve any mucocutaneous surface, it does have a predilection for keratinized tissue, with the tongue and cutaneous lip commonly involved.[2,3] Our patient had a solitary linear erosion on the dorsal aspect of the tongue, but the rest of the oral cavity was strikingly spared. In addition, the erosions around the

mouth stopped right at the cutaneous lip, sparing the labial mucosa (Figure 1B).

Second, the configuration of the erosions on the trunk, arms, and legs was diagnostic. Herpes classically presents as a cluster of vesicles overlying an erythematous base. When these vesicles rupture, punched-out erosions are left behind. Because these vesicles often are grouped, they can develop a scalloped border, which is a helpful indicator of HSV (Figure 1C). When these erosions become more confluent and irregular, the distinction from other conditions may not be as clear. A careful skin examination often can show areas that have preserved this herpetiform configuration.

Immune Compromise—Additionally, this case is illustrative of how immunosuppression and immunocompromise can affect the clinical presentation of HSV infection. Herpetic infections in the immunocompromised host tend to have a more protracted course, with chronic enlarging ulcers involving multiple sites. Furthermore, the morphology often is atypical, with ulcerodestructive, pustular, exophytic, and verrucous features as illustrated in this case. It is important to be mindful of these characteristics of HSV to properly diagnose an immunocompromised host.

Conclusion

This case is a good reminder that not everything that blisters and involves the mucosa is due to a hypersensitivity state such as TEN and Stevens-Johnson syndrome or an immunobullous disorder such as pemphigus vulgaris and pemphigus vegetans. The fact that this patient was worsening despite drug cessation, high-dose steroids, and IV immunoglobulin should have indicated a misdiagnosis. This case also shows that the early histopathologic findings of disseminated HSV and TEN can be nonspecific, and viral cytopathic changes may not always be obvious early in the disease.

Disseminated HSV should be considered in the differential diagnosis of a patient with an acute blistering eruption with mucosal involvement, and careful history and physical examination should be taken to rule out a viral etiology.

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