

Asboe-Hansen Sign in Toxic Epidermal Necrolysis

Jessica R. Dowling, BA; Kathryn L. Anderson, MD; William W. Huang, MD, MPH

PRACTICE POINTS

- Asboe-Hansen sign is a useful clinical tool for diagnosing toxic epidermal necrolysis (TEN).
- Asboe-Hansen sign can be employed to generate a fresh bulla for lesional skin biopsy in the evaluation of TEN.

To the Editor:

A 25-year-old woman with no notable medical history was admitted to the hospital for suspected Stevens-Johnson syndrome (SJS). The patient was started on amoxicillin 7 days prior to the skin eruption for prophylaxis before removal of an intrauterine device. On the day of admission, she reported ocular discomfort, dysphagia, and dysuria. She developed erythema of the conjunctivae, face, chest, and proximal upper extremities, as well as erosions of the vermilion lips. She presented to the local emergency department and was transferred to our institution for urgent dermatologic consultation. On physical examination by the dermatology service, the patient had erythematous macules coalescing into patches with overlying flaccid bullae, some denuded, involving the face, chest, abdomen, back (Figure 1), bilateral upper extremities, bilateral thighs, and labia majora and minora. Additionally, she had conjunctivitis, superficial erosions of the vermilion lips, and tense bullae of the palms and soles. On palpation of the flaccid bullae, the Asboe-Hansen sign was elicited (Figure 2 and video). A shave biopsy of the newly elicited bullae was performed. Pathology showed a subepidermal bulla with confluent necrosis of the epidermis and minimal inflammatory infiltrate. An additional shave biopsy of perilesional skin was obtained for direct

immunofluorescence, which was negative for IgG, C3, IgM, and IgA. Based on the clinical presentation involving more than 30% of the patient's body surface area (BSA) and the pathology findings, a diagnosis of toxic epidermal necrolysis (TEN) was made. The patient remained in the intensive care unit with a multidisciplinary team consisting of dermatology, ophthalmology, gynecology, gastroenterology, and the general surgery burn group. Following treatment with intravenous immunoglobulin, systemic corticosteroids, and aggressive wound care, the patient made a full recovery.

Toxic epidermal necrolysis is a rare, acute, life-threatening mucocutaneous disease within a spectrum of adverse cutaneous drug reactions. The estimated worldwide incidence of TEN is 0.4 to 1.9 per million individuals annually.¹ Toxic epidermal necrolysis is clinically characterized by diffuse exfoliation of the skin and mucosae with flaccid bullae. These clinical features are a consequence of extensive keratinocyte death, leading to dermoepidermal junction dissociation. Commonly, there is a prodrome of fever, pharyngitis, and painful skin preceding the diffuse erythema and sloughing of skin and mucous membranes. Lesions typically first appear on the trunk and then follow a centrifugal spread, often sparing the distal aspects of the arms and legs.

Toxic epidermal necrolysis is part of a continuous spectrum with SJS. Less than 10% BSA involvement is considered SJS, 10% to 30% BSA involvement is

RELATED VIDEO ONLINE

A video demonstrating the Asboe-Hansen sign is available with this article online

>> www.mdedge.com/dermatology

Ms. Dowling is from the Charles E. Schmidt College of Medicine, Florida Atlantic University, Boca Raton. Drs. Anderson and Huang are from the Department of Dermatology, Wake Forest School of Medicine, Winston-Salem, North Carolina.

The authors report no conflict of interest.

The video is available online at www.mdedge.com/dermatology.

Correspondence: Kathryn L. Anderson, MD, Department of Dermatology, Wake Forest School of Medicine, Medical Center Blvd, Winston-Salem, NC 27157-1071 (klanders@wakehealth.edu).



FIGURE 1. Erythematous macules coalescing into large patches with overlying flaccid and denuded bullae in the setting of toxic epidermal necrolysis.



FIGURE 2. To elicit the Asboe-Hansen sign, perpendicular pressure is applied to an intact bulla.

SJS/TEN overlap, and more than 30% BSA detachment is TEN. Stevens-Johnson syndrome can progress to TEN. In TEN, the distribution of cutaneous lesions is more confluent, and mucosal involvement is more severe.² The differential diagnosis may include staphylococcal scalded skin syndrome, drug-induced linear IgA bullous dermatosis, severe acute graft-vs-host disease, drug reaction with eosinophilia and systemic symptoms, and invasive fungal dermatitis. An accurate diagnosis of TEN is imperative, as the management and morbidity of these diseases are vastly different. Toxic epidermal necrolysis has an estimated mortality rate of 25% to 30%, with sepsis leading to multiorgan failure being the most common cause of death.³

Although the pathophysiology of TEN has yet to be fully elucidated, it is thought to be a T cell-mediated process with CD8⁺ cells acting as the primary means of keratinocyte death. An estimated 80% to 95% of cases are due to drug reactions.³ The medications that are most commonly associated with TEN include allopurinol, antibiotics, nonsteroidal anti-inflammatory drugs, and anti-convulsants. Symptoms typically begin 7 to 21 days after starting the drug. Less commonly, *Mycoplasma pneumoniae*, dengue virus, cytomegalovirus, and contrast medium have been reported as inciting factors for TEN.²

The diagnosis of TEN is established by correlating clinical features with a histopathologic examination

obtained from a lesional skin biopsy. The classic cutaneous features of TEN begin as erythematous, flesh-colored, dusky to violaceous macules and/or morbilliform or targetoid lesions. These early lesions have the tendency to coalesce. The cutaneous findings will eventually progress into flaccid bullae, diffuse epidermal sloughing, and full-thickness skin necrosis.^{2,3} The evolution of skin lesions may be rapid or may take several days to develop. On palpation, the Nikolsky (lateral shearing of epidermis with minimal pressure) and Asboe-Hansen sign will be positive in patients with SJS/TEN, demonstrating that the associated blisters are flaccid and may be displaced peripherally.⁴ For an accurate diagnosis, the biopsy must contain full-thickness epidermis. It is imperative to choose a biopsy site from an acute blister, as old lesions of other diseases, such as erythema multiforme, will eventually become necrotic and mimic the histopathologic appearance of SJS/TEN, potentially leading to an incorrect diagnosis.⁴ Full-thickness epidermal necrosis has a high sensitivity but low specificity for TEN.³ The histologic features of TEN vary depending on the stage of the

disease. Classic histologic findings include satellite necrosis of keratinocytes followed by full-thickness necrosis of keratinocytes and perivascular lymphoid infiltrates. The stratum corneum retains its original structure.⁴

The Asboe-Hansen sign, also known as the bulla spread sign, was originally described in 1960 as a diagnostic sign for pemphigus vulgaris.⁵ A positive Asboe-Hansen sign demonstrates the ability to enlarge a bulla in the lateral direction by applying perpendicular mechanical pressure to the roof of an intact bulla. The bulla is extended to adjacent nonblistered skin.⁶ A positive sign demonstrates decreased adhesion between keratinocytes or between the basal epidermal cells and the dermal connective tissue.⁵ In addition to pemphigus vulgaris, the Asboe-Hansen sign may be positive in TEN and SJS, as well as other diseases affecting the dermoepidermal junction including pemphigus foliaceus, pemphigus vegetans, and bullous pemphigoid. Asboe-Hansen⁵ made the argument that a fresh bulla should be biopsied if histopathologic diagnosis is necessary, as older bullae may exhibit epithelial cell regeneration and disturb an accurate diagnosis.

Accurate and early diagnosis of TEN is imperative, as prognosis is strongly correlated with the speed at which the offending drug is discontinued and appropriate medical treatment is initiated. Prompt withdrawal of the offending drug has been reported to reduce the risk for

morbidity by 30% per day.⁷ Although classically associated with the pemphigus group of diseases, the Asboe-Hansen sign is of diagnostic value to the pathologist in diagnosing TEN by reproducing the same microscopic appearance of a fresh spontaneous blister. Due to the notable morbidity and mortality in SJS and TEN, the Asboe-Hansen sign should be attempted for the site of a lesional biopsy, as an accurate diagnosis relies on clinicopathologic correlation.

REFERENCES

1. Schwartz RA, McDonough PH, Lee BW, et al. Toxic epidermal necrolysis: part I. introduction, history, classification, clinical features, systemic manifestations, etiology, and immunopathogenesis. *J Am Acad Dermatol.* 2013;69:173.e1-173.e13.
2. Frech LE, Prins C. Erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. In: Bologna J, Jorizzo J, Schaffer J, eds. *Dermatology.* 3rd ed. New York, NY: Elsevier; 2012:332-347.
3. Schwartz RA, McDonough PH, Lee BW, et al. Toxic epidermal necrolysis: part II. prognosis, sequelae, diagnosis, differential diagnosis, prevention, and treatment. *J Am Acad Dermatol.* 2013;69:187.e1-187.e16.
4. Elston D, Stratman E, Miller S. Skin biopsy. *J Am Acad Dermatol.* 2016;74:1-16.
5. Asboe-Hansen G. Blister-spread induced by finger-pressure, a diagnostic sign in pemphigus. *J Invest Dermatol.* 1960;34:5-9.
6. Ganapati S. Eponymous dermatological signs in bullous dermatoses. *Indian J Dermatol.* 2014;59:21-23.
7. Garcia-Doval I, Lecleach L, Bocquet H, et al. Toxic epidermal necrolysis and Stevens-Johnson syndrome: does early withdrawal of causative drugs decrease the risk of death? *Arch Dermatol.* 2000;136:323-327.