Immunodeficiency and post-operative antibiotic use leading to development of toxic epidermal necrolysis

Patrina Agosta, Sophia Halassy, Sharon Miller, Sayeh Nabati

ABSTRACT

Introduction: The rarity of Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) often lead to a missed diagnosis of a severe, life-threatening disease spectrum. Major risk factors include immunodeficiency and use of certain medications. Patients often present with fever and mucositis which can quickly lead to skin sloughing rash. Rapid diagnosis, treatment, and transfer to the Intensive Care or Burn Unit are essential preventing morbidity and mortality.

Case Report: Our case presents a patient whose initial complaint consisted of poorly controlled pain from a primary herpetic outbreak. Her hospital course eventually led to an unrelenting fever, oral lesions, and rash along her neck and chest which encompassed her entire body within 12 hours and led to sloughing of her areola and labia, and even labial agglutination. Rapid transfer to a Burn Unit, aggressive fluid hydration, and close monitoring were critical in her care.

Conclusion: The rapid progression and high morbidity and mortality rates make it important for healthcare personnel to recognize SJS quickly. Obstetricians and Gynecologists especially should have heightened awareness as the failure to provide a gynecologic exam can have devastating effects. Every patient with signs or symptoms of SJS, especially those with risk factors such as immunocompromise or use of specific medications, should undergo a prompt and thorough workup.

Keywords: Herpes simplex virus, Nitrofurantoin, Stevens–Johnson syndrome, Toxic epidermal necrolysis

INTRODUCTION

Steven–Johnson syndrome (SJS), albeit rare, is a condition that if not recognized early can have detrimental effects. The field of Obstetrics and Gynecology involves a number of ulcerative cutaneous lesions involving the mucous membranes. A wide differential diagnosis should be formulated when these conditions are encountered. We present a case in which a woman was diagnosed with a primary herpes outbreak based on clinical presentation and serology. Whether it was actually a primary herpes simplex virus (HSV) outbreak or SJS which was mistaken for a primary herpes outbreak leading to an immunocompromised status and then SJS or SJS which was mistaken for a primary herpes simple virus (HSV) outbreak, the signs and symptoms or SJS should be familiar to every Obstetrician and Gynecologist.

CASE REPORT

A 40-year-old G7 P6-0-1-7 female initially presented to the office with a primary complaint of painful
urination, vaginal burning, and irritation. On examination, vesicular lesions were noted, a culture for herpes simplex virus (HSV) and other sexually transmitted infections (STIs) was collected. Given that this was the first of such occurrences for the patient, she had been given a diagnosis of primary HSV outbreak and was given prescriptions for topical lidocaine jelly and Valacyclovir. During the same office visit, the patient was noted to have slight erythema and induration at a laparoscopic port-site incision after having undergone a right-sided salpingectomy for ectopic pregnancy 15 days prior to this current office visit. She was given a prescription for Nitrofurantoin. Despite proper compliance, the vulvar pain persisted and the patient later developed chills and a febrile episode of 102 degrees Fahrenheit (°F) at home two days after her office visit, prompting her to present to the emergency department for further evaluation.

At the time of emergency department evaluation, her vital signs were stable, and her surgical incision was noted to be without signs of infection. External genitalia examination demonstrated extensive vulvar vesicular lesions consistent with herpetic outbreak. A minority of the vesicles was surrounded by erythema, and expressed purulent discharge. The patient did not have evidence of leukocytosis. Review of previous in-office culture results was negative for herpes or other STIs. Regardless, she was admitted to the hospital for pain management with Lidocaine jelly, Ketorolac, and Hydrocortisone/Acetaminophen, as needed, and continued on Valacyclovir.

Other than her history as highlighted above, the patient had a history of five full-term vaginal deliveries and one full-term cesarean section due to twin gestation. Her last menstrual period was approximately one month before, and she had a pertinent gynecological history of chlamydia infection in the past, which was successfully treated. Her medical history was significant for asthma, and she had not undergone any other surgery other than previously described.

During in-hospital stay, the patient had complained of a sore throat and upper respiratory infection-like symptoms. She was given Chloraseptic spray, menthol lozenges, and Pseudoephedrine for relief. The patient was also prescribed moisturizing eyedrops for conjunctival irritation. She was noted to have decreasing leukopenia from 5.1 to 3.9 K/mcL. Herpes simplex virus serology was positive for both immunoglobulin (Ig) G and IgM. A rapid Streptococcus test was negative. On the evening of hospital day 3, the patient had a low-lying fever of 100.8 °F along with some tachycardia. An Internal Medicine consultation was placed for further evaluation. Physical examination findings were significant for mild papular skin rash in the upper trunk and neck area. A working diagnosis of viral syndrome was made. The patient was started on aggressive intravenous (IV) fluid hydration and Ceftriaxone until final upper respiratory cultures resulted. Due to her myriad and acute worsening of symptoms, a human immunodeficiency virus (HIV) and hepatitis panel was also obtained. Infectious disease was consulted.

The following day, there was rapid decompensation in the patient state. She was noted to have an accelerated progression of a bullous, erythematous rash, encompassing the patient’s face and upper chest. The patient had severe conjunctival infection of both eyes with associated blurry vision. She was noted to have severe tachycardia, and persistent fever with max temperature of 103 °F, despite repeated Acetaminophen administration. With a working diagnosis of sepsis, the patient was placed in the Intensive Care Unit (ICU) with aggressive fluid management. She was started on Vancomycin, Piperacillin/Tazobactam and the Valacyclovir was discontinued due to fear of drug reaction. The patient was given Methylprednisolone and she was closely monitored. Workup included computerized tomography (CT) of the abdomen and pelvis, which were negative. All serum laboratory values and cultures were within normal limits, except for mild elevation in inflammatory markers (e.g., C-reactive protein and erythrocyte sedimentation rate).

The next day, the patient was noted to have significant mucocutaneous progression. The rash spread quickly, and there was gross sloughing of the right labia minora and right areola. The patient had labial agglutination, diffuse maculopapular rash with sloughing, bilateral conjunctival injection with erythema and swelling of bilateral eyelids, encompassing more than 40% of her body in totality. A final diagnosis of toxic epidermal necrolysis (TEN) was made. Due to quick and rapid deterioration of the patient, the patient was transferred to a primary hospital site’s specialized burn unit for further care.

**DISCUSSION**

Stevens–Johnson syndrome is a rare phenomenon, so rare that according to a global population-based study, the incidence is estimated to be only 1.0–6.0 per million [1]. The incidence appears to be greater in immunocompromised patients, especially those with HIV and cancer [2, 3]. It is more prevalent in the female population with a 2:1 ratio [4]. Our case involved an adult female who may have had an altered immunity after surgery, and have led to the development of her primary herpetic outbreak.

Stevens–Johnson syndrome is the result of a type IV hypersensitivity reaction [5] and its pathogenesis is not completely understood. In general, it is thought to be due to dysregulation of cellular immunity [6]. This dysregulation causes activation of cytotoxic T and natural killer cells [7] which release various cytotoxic signals including granulysin [8], perforin/granzyme B, and Fas/Fas ligand [9] which take effect on keratinocytes [10]. This leads to detachment of the epidermis due to extensive necrosis [11]. Stevens–Johnson syndrome is considered a disease continuum with increasing severity progressing to TEN. It involves skin detachment of <10% of the body surface and progression to TEN involves detachment of >30% of body surface area [12, 13], such as our patient, who also had
mucosal membrane involvement. Muco-cutaneous involvement is a common finding in SJS and can lead to severe complications, including infections, malnutrition, and dehydration.

Clinical presentations often mirror flu-like prodrome including malaise, myalgia, and arthralgia with a high fever which can exceed 102.0. These symptoms often present one to three days prior to mucocutaneous lesions [23]. In our case, mucositis lesions developed within 12 hours of her febrile illness. Cutaneous lesions often start as an erythematous rash that progresses to coalescing macules or targetoid lesions with purpuric centers [24, 25]. These lesions typically start on the face and spread down to the thorax, most often sparing the scalp, palms, and soles [26, 27], such as our case and slough off with a light touch known as the “nikolsky sign.” Our patient had sloughing of her areola and vulvar epithelium with only light touch.

Stevens–Johnson syndrome is primarily a clinical diagnosis; however, workup can include a number of tests. Laboratory work includes complete blood count with differential, metabolic panel, erythrocyte sedimentation rate, and C-reactive protein. Blood and mucosal lesion cultures can be obtained as patients are at high risk of sepsis due to skin sloughing and exposed membranes. A chest radiograph should be obtained in all patients [35]. A skin biopsy for histopathologic examination and direct immunofluorescence can aid in confirming diagnosis.

A skin biopsy for histopathologic examination and direct immunofluorescence can aid in confirming diagnosis. Apoptotic keratinocytes scattered throughout the basal layer of the epidermis; however, this should be noted that this is a finding that can be seen in other conditions as well. Direct immunofluorescence is always negative [11].

Severity and prognosis of SJS depends upon the percentage of body surface area involved in the amount of skin sloughing [35]. The severity and prognosis of a patient with SJS can be determined using the SCORTEN scale [36]. Individual prognostic factors are given a point and the overall score is associated with a corresponding mortality rate. The score for our patient was 3 (notably serum bicarbonate=15 mEq/L, heart rate=140 beats per minute, involved body surface area >30%), indicating a 35% mortality rate and diagnosis of TEN.

A key aspect in the treatment of SJS is identification and withdrawal of the offending agent if one can be identified [37]. Patients should be treated in a hospital setting, particularly in an intensive care unit if possible [38, 39]. Supportive care is the main goal and includes fluid and electrolyte replacement, pain control, and treatment of concomitant infections [40–42]. While sepsis and superinfections are prominent and remain one of the leading causes of death, systemic antibiotics are not advised or employed universally and should be used based on individual cultures [43]. Special attention should be paid to identifying ocular for immediate treatment as effects can be detrimental. Early gynecologic exam is important and one that can be easily missed. Steven–Johnson syndrome increases the risk of vulvovaginal adhesions as well as metaplastic changes of tissue. The use of intravaginal corticosteroids and soft vaginal dilators can aid in the prevention of adhesions [44].

CONCLUSION

It is important for all healthcare personnel to be aware of SJS as it is a disease that can easily be mistaken or missed in its early stages. Its rapid progression and associated morbidity and mortality should prompt early investigation and treatment. Obstetricians and Gynecologists should have a heightened awareness as the failure to provide a gynecologic exam can have devastating effects and could even lead to patient death. Any patient with important risk factors such as immunodeficiency and recent use of antibiotics presenting with rash and febrile episode should undergo a proper workup.

REFERENCES

1. Chan HL, Stern RS, Arndt KA, et al. The incidence of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. A population-based study with particular reference to reactions caused by drugs among outpatients. Arch Dermatol 1990;126(1):43–7.
2. Mittmann N, Knowles SR, Koo M, Shear NH, Rachlis A, Rourke SB. Incidence of toxic epidermal necrolysis and Stevens-Johnson syndrome in an HIV cohort: An observational, retrospective case series study. Am J Clin Dermatol 2012;13(1):49–54.
3. Gillis NK, Hicks JK, Bell GC, Daly AJ, Kanetsky PA, McLeod HL. Incidence and Triggers of Stevens-Johnson syndrome and toxic epidermal necrolysis in a large cancer patient cohort. J Invest Dermatol 2017;137(9):2021–3.
4. Sekula P, Dunant A, Mockenhaupt M, et al. Comprehensive survival analysis of a cohort of patients with Stevens-Johnson syndrome and toxic epidermal necrolysis. J Invest Dermatol 2013;133(5):1197–204.

5. Roujeau JC. Immune mechanisms in drug allergy. Allergol Int 2006;55(1):27–33.

6. Su SC, Mockenhaupt M, Wolkenstein P, et al. Interleukin-15 is associated with severity and mortality in Stevens-Johnson syndrome/toxic epidermal necrolysis. J Invest Dermatol 2017;137(5):1065–73.

7. Chung WH, Wang CW, Dao RL. Severe cutaneous adverse drug reactions. J Dermatol 2016;43(7):758–66.

8. Chung WH, Hung SI, Yang JY, et al. Granulysin is a key mediator for disseminated keratinocyte death in Stevens-Johnson syndrome and toxic epidermal necrolysis. Nat Med 2008;14(12):1343–50.

9. Posadas SJ, Padial A, Torres MJ, et al. Delayed reactions to drugs show levels of perforin, granzyme B, and Fas-L to be related to disease severity. J Allergy Clin Immunol 2002;109(1):155–61.

10. Correia O, Delgado L, Ramos JP, Resende C, Torrinha JA. Cutaneous T-cell recruitment in toxic epidermal necrolysis. Further evidence of CD8+ lymphocyte involvement. Arch Dermatol 1993;129(4):466–8.

11. Rzany B, Hering O, Mockenhaupt M, et al. Histopathological and epidemiological characteristics of patients with erythema exudativum multiforme major, Stevens-Johnson syndrome and toxic epidermal necrolysis. Br J Dermatol 1996;135(1):6–11.

12. Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau JC. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. Arch Dermatol 1993;129(1):92–6.

13. Roujeau JC. Stevens-Johnson syndrome and toxic epidermal necrolysis are severity variants of the same disease which differs from erythema multiforme. J Dermatol 1997;24(11):726–9.

14. Sassolas B, Haddad C, Mockenhaupt M, et al. ALDEN, an algorithm for assessment of drug causality in Stevens-Johnson syndrome and toxic epidermal necrolysis: Comparison with case-control analysis. Clin Pharmacol Ther 2010;88(1):60–8.

15. Levi N, Bastuji-Garin S, Mockenhaupt M, et al. Medications as risk factors of Stevens-Johnson syndrome and toxic epidermal necrolysis in children: A pooled analysis. Pediatrics 2009;123(2):e297–304.

16. Hertz S. Challenge of Developing New Pain Medicines - Developing Novel Analgesics and Abuse-Deterrent Opioid Formulations. Silver Spring, MD: Science Board to the Food and Drug Administration; 2016.

17. Mockenhaupt M, Viboud C, Dunant A, et al. Stevens-Johnson syndrome and toxic epidermal necrolysis: Assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR-study. J Dermatol 2008;128(8):35–44.

18. KoTM, Chung WH, WeiCY, et al. Shared and restricted T-cell receptor use is crucial for carbamazepine-induced Stevens-Johnson syndrome. J Allergy Clin Immunol 2011;128(6):1266–76.e11.

19. Tangamornsuksn W, Chaiyakunapruk N, Somkrua R, Lohitnavy M, Tassaneeyakul W. Relationship between the HLA-B*1502 allele and carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis: A systematic review and meta-analysis. JAMA Dermatol 2013;149(9):1025–32.

20. McCormack M, Alfrevic A, Bourgeois S, et al. HL-A*A*3101 and carbamazepine-induced hypersensitivity reactions in Europeans. N Engl J Med 2011;364(12):1134–43.

21. Somkrua R, Eickman EE, Saokaew S, Lohitnavy M, Chaiyakunapruk N. Association of HLA-B*5701 allele and allopurinol-induced Stevens-Johnson syndrome and toxic epidermal necrolysis: A systematic review and meta-analysis. BMC Med Genet 2011;12:118.

22. Shen Y, Niccoletti F, Floratos A, et al. Genome-wide association study of serious blistral drug rash caused by drugs. Pharmacogenomics J 2012;12(2):96–104.

23. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. N Engl J Med 1994;331(19):1272–85.

24. Schwartz RA, McDonough PH, Lee BW. Toxic epidermal necrolysis: Part I. Introduction, history, classification, clinical features, systemic manifestations, etiology, and immunopathogenesis. J Am Acad Dermatol 2013;69(2):173.e1–13.

25. Valeisy-Allanore L, Roujeau JC. Epidermal necrolysis (stevens-johnson syndrome and toxic epidermal necrolysis). In: Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell D, Wolff K, editors. Fitzpatrick’s Dermatology in General Medicine. 8ed. New York: McGraw Hill; 2012. p. 439–48.

26. Ruiz-Maldonado R. Acute disseminated epidermal necrosis types 1, 2, and 3: Study of sixty cases. J Am Acad Dermatol 1985;13(4):623–35.

27. Revuz J, Roujeau JC, Guilhaume JC, Penso D, Touraine R. Treatment of toxic epidermal necrolysis. Cerite’s experience. Arch Dermatol 1987;123(9):1156–8.

28. Letko E, Papaliodis DN, Papaliodis GN, Daoud YJ, Ahmed AR, Foster CS, Stevens-Johnson syndrome and toxic epidermal necrolysis: A review of the literature. Ann Allergy Asthma Immunol 2005;94(4):419–36.

29. Meneux E, Wolkenstein P, Haddad B, Roujeau JC, Revuz J, Paniel BJ. Vulvovaginal involvement in toxic epidermal necrolysis: A retrospective study of 40 cases. Obstet Gynecol 1998;91(2):283–7.

30. de Prost N, Mekontso-Dessap A, Valeisy-Allanore L, et al. Acute respiratory failure in patients with toxic epidermal necrolysis: Clinical features and factors associated with mechanical ventilation. Crit Care Med 2014;42(1):118–28.

31. Morales ME, Purdue GF, Veity SM, Arnoldo BD, Blomquist PH. Ophthalmic manifestations of Stevens-Johnson syndrome and toxic epidermal necrosis and relation to SCORTEN. Am J Ophthalmol 2010;150(4):505–10.e1.

32. Guedry J, Roujeau JC, Binaghi M, Soubrane G, Muraine M. Risk factors for the development of ocular complications of Stevens-Johnson syndrome and toxic epidermal necrolysis. Arch Dermatol 2009;145(2):157–62.

33. Pliskow S. Severe gynecologic sequelae of Stevens-Johnson syndrome and toxic epidermal necrolysis caused by ibuprofen: A case report. J Reprod Med 2013;58(7–8):354–6.

34. Bircher AJ. Symptoms and danger signs in acute drug hypersensitivity. Toxicology 2005;209(2):201–7.
Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau JC, Revuz J, Wolkenstein P. SCORTEN: A severity-of-illness score for toxic epidermal necrolysis. J Invest Dermatol 2000;115(2):149–53.

36. Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau JC, Revuz J, Wolkenstein P. SCORTEN: A severity-of-illness score for toxic epidermal necrolysis. J Invest Dermatol 2000;115(2):149–53.

37. Garcia-Doval I, LeCleach L, Bocquet H, Otero XL, Roujeau JC. Toxic epidermal necrolysis and Stevens-Johnson syndrome: Does early withdrawal of causative drugs decrease the risk of death? Arch Dermatol 2000;136(3):323–7.

38. Creamer D, Walsh SA, Dziewulski P, et al. U.K. guidelines for the management of Stevens-Johnson syndrome/toxic epidermal necrolysis in adults 2016. Br J Dermatol 2016;174(6):1194–227.

39. Harr T, French LE. Toxic epidermal necrolysis and Stevens-Johnson syndrome. Orphanet J Rare Dis 2010;5:39.

40. Roujeau JC, Chosidow O, Saïag P, Guillaume JC. Toxic epidermal necrolysis (Lyell syndrome). J Am Acad Dermatol 1990;23(6 Part 1):1039–58.

41. Struck MF, Illert T, Liss Y, Bosbach ID, Reichelt B, Steen M. Toxic epidermal necrolysis in pregnancy: case report and review of the literature. J Burn Care Res 2010;31(5):816–21.

42. Schwartz RA, McDonough PH, Lee BW. Toxic epidermal necrolysis: Part II. Prognosis, sequelae, diagnosis, differential diagnosis, prevention, and treatment. J Am Acad Dermatol 2013;69(2):187.e1–16; quiz 203–4.

43. Palmieri TL, Greenhalgh DG, Saffle JR, et al. A multicenter review of toxic epidermal necrolysis treated in U.S. burn centers at the end of the twentieth century. J Burn Care Rehabil 2002;23(2):87–95.

44. Kaser DJ, Reichman DE, Laufer MR. Prevention of vulvovaginal sequelae in Stevens-Johnson syndrome and toxic epidermal necrolysis. Rev Obstet Gynecol 2011;4(2):81–5.

Author Contributions
Patrina Agosta – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Sophia Halassy – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Sharon Miller – Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Sayeh Nabati – Acquisition of data, Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission
The corresponding author is the guarantor of submission.

Source of Support
None.

Consent Statement
Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest
Authors declare no conflict of interest.

Data Availability
All relevant data are within the paper and its Supporting Information files.

Copyright
© 2021 Patrina Agosta et al. This article is distributed under the terms of Creative Commons Attribution License which permits unrestricted use, distribution and reproduction in any medium provided the original author(s) and original publisher are properly credited. Please see the copyright policy on the journal website for more information.
| Access full text article on other devices | Access PDF of article on other devices |
|------------------------------------------|--------------------------------------|

![QR Code for Access Full Text](image1)

![QR Code for Access PDF](image2)
Submit your manuscripts at
www.edoriumjournals.com