Journal of HOSPITAL MEDICINE www.journalofhospitalmedicine.com

CASE REPORT

Toxic Epidermal Necrolysis (TEN) Associated With Herbal Medication Use in a Patient With Systemic Lupus Erythematosus

Vagish Hemmige, MD[1]
Erin Jenkins, MD[1]
Jhee Un Lee, MD[2]
Vineet M. Arora, MA, MD[1]

[1] Department of Medicine, University of Chicago, Chicago, Illinois.
[2] Department of Medicine, Emory University, Atlanta, Georgia.

Disclosure: Nothing to report.

KEYWORDS: complementary and alternative medicine, drug toxicity, herbal medication, systemic lupus erythematosus, toxic epidermal necrolysis.

A 49-year-old woman with history of rheumatic fever necessitating mechanical mitral valve replacement and a cerebrovascular accident of presumed embolic etiology presented with several months of progressive fatigue, weakness, arthralgias, and myalgias. After an extensive workup, a rheumatologist in the community diagnosed her with systemic lupus erythematosus and dermatomyositis. The patient refused therapy with corticosteroids and disease-modifying agents, citing concerns of adverse effects. She consulted a naturopathic clinician, who gave her Rejuvenator Pills, Super Booster pill, Genesis Juice, and alkaline water (Table 1).

Several weeks later, the patient developed dusky erythematous plaques on her anterior and posterior trunk, face, and proximal extremities. Over the next several weeks, she became progressively weak until she was ultimately bedbound. The plaques over her back began to denude. Upon admission to an outside hospital, she was diagnosed with warfarin-related skin necrosis, superinfected decubitus ulcers, and severe anemia. She refused blood transfusion, and was discharged home with clindamycin and iron. After her clinical status deteriorated over the subsequent week, she arrived at our hospital by ambulance.

In addition to the herbal medications she had recently started, she had been taking warfarin, furosemide, nitroglycerin via skin patch, and aspirin for over 10 years. On exam, she was febrile, tachycardic, hypotensive, and toxic-appearing. Conjunctivitis was absent. Her mucous membranes were dry, with easily removable white and yellowish deposits on the buccal mucosa. No lesions or ulcerations were present. Dermatologic exam demonstrated confluent scaly, violaceous erythematous patches and plaques covering 60% of the total body surface area with focal areas that were denuded. Large areas of denuded skin were present over the back, inframammary folds, and underneath her abdominal pannus (Figures 1 and 2). Nikolsky's sign was present. She was oriented to person only.

Initial laboratory studies were significant for the following: white blood cell count = 12,800 cells/mm^3, hemoglobin = 7.3 g/dL, creatinine = 11.2 mg/dL, blood urea nitrogen = 136 mg/dL, and bicarbonate level = 15 mmol/L. She was admitted to the medical intensive care unit for presumed sepsis. Aggressive resuscitation and broad spectrum antibiotics were administered. A thorough workup for infection, including blood and urine cultures, chest radiography, and lumbar puncture, was unremarkable. Antinuclear antibodies (ANAs) were present in a 1:2560 titer; with a nucleolar and speckled pattern and cytoplasmic antibodies. Additional rheumatologic workup revealed positive anti-Smith antibody and weakly positive antiribonuclear protein antibody. Pathology from a punch biopsy performed by a dermatology consultant on hospital day 2 demonstrated full-thickness skin necrosis with scant perivascular infiltrate. While the patient's family had disposed of the pill containers, they had kept several pills. These were sent for analysis, which did not reveal contamination with heavy metals or allopathic medications.

The patient was ultimately diagnosed with TEN and systemic lupus erythematosus with overlap syndrome, and intravenous methylprednisolone was administered. Broad-spectrum antibiotics were administered for 48 hours, but stopped after workup for infection proved unrevealing. Wound care was mupirocin ointment with petrolatum dressings twice daily as per the hospital's TEN protocol. The patient's course was complicated by acidosis requiring hemodialysis and several tonic-clonic seizures, a result of presumed lupus cerebritis due to rapidly progressive lesions on serial magnetic resonance images (MRIs) with a negative lumbar puncture. Renal biopsy demonstrated acute tubular necrosis and collapsing glomerulopathy. The patient ultimately recovered, and was discharged to a rehabilitation facility. In follow-up several months later, she had healing skin with residual dyspigmentation and normal renal function. She was ambulatory and fully oriented, but complained of persistent memory difficulties.

Discussion

While use of complementary or alternative medicine (CAM) is widespread, physicians often underestimate the

2010 Society of Hospital Medicine DOI 10.1002/jhm.639
View this article online at wileyonlinelibrary.com.

TABLE 1. Ingredients in the Herbal Medications

Rejuvenator Pill
Slippery elm 45 mg (*Ulmus rubra*)
Capsicum 40 mg (*Capsicum* spp.)
Fennel seeds 35 mg (*Foeniculum vulgare*)
Chickweed 35 mg (*Stellaria media*)
Hawthorn berry 30 mg (*Crataegus oxyacantha*)
Mullein 30 mg (*Verbascum thapsus*)
Scullcap 25 mg (*Scutellaria* spp.)
Rosehip 25 mg (*Rosa* spp.)
Barberry 20 mg (*Berberis vulgaris*)
Pau d'arco 20 mg (*Tabebuia* spp.)
Comfrey leaf 20 mg (*Symphytum officinale*)
Alfalfa 20 mg (*Medicago sativa*)
Kelp 20 mg (*Laminaria* spp.)
Papaya leaf 15 mg (*Carica papaya*)
Bee pollen 15 mg
Black cohosh 15 mg (*Cimicifuga racemosa*)
Chaparral 10 mg (*Larrea tridentata*)
Ginger 10 mg (*Zingiber officinale*)
Dandelion 5 mg (*Taraxacum officinale*)
Sunflower 5 mg (*Helianthus annuus*)
Licorice root 5 mg (*Glycyrrhiza glabra*)
Cascara sagrada 25 mg
Super Booster pill
Cascara sagrada
Psyllium (*Plantago* spp.)
Fennel (*Foeniculum vulgare*)
Genesis Juice
Apple (*Malus domestica*)
Pomegranate (*Punica granatum*)
Aloe vera juice (reconstituted)
Whole fruit grape extract (*Vitis vinifera* spp.)
Barley grass (*Hordeum vulgare*)
Cinnamon bark (*Cinnamomum* spp.)
Coriander leaf (*Coriandrum sativum*)
Coriander seed (*Coriandrum sativum*)
Cucumber (*Cucumis sativus*)
Fig fruit (*Ficus carica*)
Garlic bulb (*Allium sativum*)
Juniper berry (*Juniperus* spp.)
Leek (*Allium ampeloprasum*)
Lentil (*Lens culinaris*)
Mulberry fruit (*Morus* spp.)
Olive leaf (*Olea europaea*)
Onion bulb (*Allium cepa*)
Sweet almond (*Prunus amygdalus dulcis*)
Wheat grass (*Triticum aestivum*)
Alkaline water

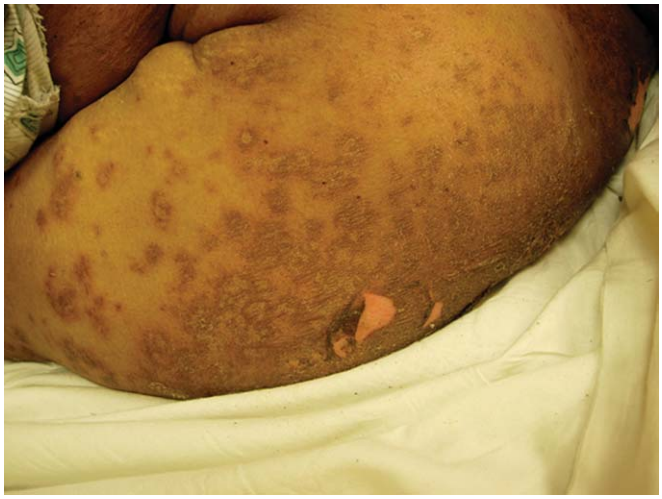

FIGURE 1. The patient on hospital day 2. The patient's back demonstrated extensive involvement with TEN, although sloughing of skin had only begun to occur. Abbreviation: TEN, toxic epidermal necrolysis.

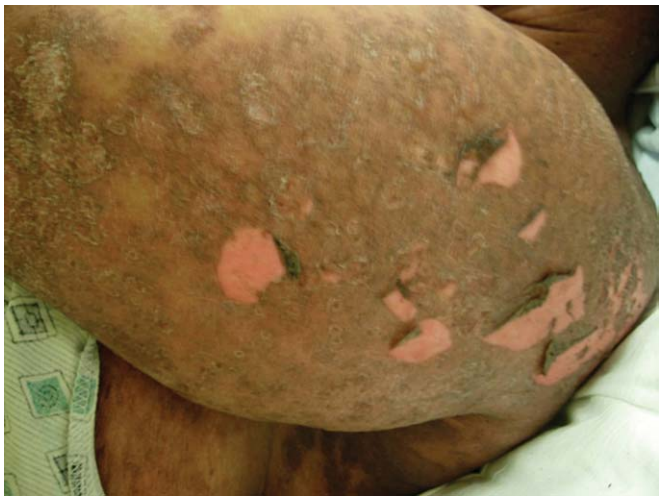

FIGURE 2. The patient on hospital day 2. The patient's arm demonstrates both a widespread erythematous rash and the presence of skin peeling with minimal trauma.

prevalence of CAM use in their patients. Only one-half of primary care practitioners are aware of the risk for serious adverse reactions from CAMs.[1] This case demonstrates the need for hospitalists to obtain a thorough medication history, including probing for CAM use, when evaluating a new patient. The delayed diagnosis of TEN, whether due to failure to elicit CAM use or recognize the clinical presentation, delayed appropriate treatment by a week and this patient developed potentially lethal complications.

Stevens-Johnson syndrome (SJS) and TEN lie on a spectrum of disorders involving separation of the epidermis from the dermis when tension is applied to the skin, associated with mucositis, conjunctivitis, and generalized toxicity. The rash is dusky and erythematous, and Nikolsky's sign (separation of the epidermis from the dermis with tension applied to the skin) is present. These entities most commonly develop secondary to medications or infections. Most reactions occur within 60 days of drug initiation. The rash progressives over 1 to 15 days, and the rate of healing is variable. The overall mortality is 30% and is predicted by the SCORTEN system, which incorporates laboratory data, patient history, and the extent of skin breakdown.[2] Treatment is primarily supportive; the use of corticosteroids, nonsteroidal immunosuppressive agents, intravenous immunoglobulin (IVIG), or plasmapheresis remains controversial.[3]

2010 Society of Hospital Medicine DOI 10.1002/jhm.639
View this article online at wileyonlinelibrary.com.

Case reports have described the development of SJS or TEN with CAM use. For example, 1 patient repeatedly developed SJS, with each episode occurring after exposure to an herbal medication containing red clover, burdock, queen's delight, poke root, prickly ash, sassafras bark, and passion flower.[4] Similar to our case, identifying the exact agent responsible for TEN was impossible due to large numbers of herbal medications combined into a single pill. SJS and TEN are not limited to Western herbal medicines. Traditional Chinese medications are one of the most common causes of SJS and TEN in East Asia,[5] although adulteration with allopathic medications is common in this setting. Ayurvedic medications,[6] an ophiopogonis-containing health drink,[7] ginseng,[8] and *Gingko biloba*[9,10] have also been implicated.

Conclusions

This case demonstrates the difficulty in making a diagnosis of CAM-induced toxicity and identifying the likely agent responsible. Hospitalists must have a high index of suspicion of CAM-associated toxicity to make this diagnosis, especially when admitting patients who may not volunteer CAM use without direct questioning.

Acknowledgements

This case was initially presented at the Midwest Society of General Internal Medicine regional meeting on September 25–26, 2008. Figures 1 and 2 are courtesy of Dr. Robert Chen. The authors thank Dr. James Rhee from the Section of Emergency Medicine at the University of Chicago, who provided toxicology consultation and assisted with toxicology analysis. The authors also acknowledge Meryl Prochaska for manuscript preparation and the patient and her family for their courage and tenacity during the recovery process.

Address for correspondence and reprint requests:
Vineet M. Arora, MD, MA, 5841 S. Maryland Ave., MC 2007, AMB W216, Chicago, IL 60637; Telephone: 773-702-8157; Fax: 773-834-2238; E-mail: varora@medicine.bsd.uchicago.edu Received 23 April 2010; revision received 24 September 2010; accepted 14 October 2010.

References

1. Giveon SM, Liberman N, Klang S, Kahan E. A survey of primary care physicians' perceptions of their patients' use of complementary medicine. *Complement Ther Med*. 2003;11(4):254–260.
2. 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):149–153.
3. Pereira FA, Mudgil AV, Rosmarin DM. Toxic epidermal necrolysis. *J Am Acad Dermatol*. 2007;56(2):181–200.
4. Monk B. Severe cutaneous reactions to alternative remedies. *Br Med J*. 1986;293(6548):665–666.
5. Khoo AK, Foo CL. Toxic epidermal necrolysis in a burns centre: a 6-year review. *Burns*. 1996;22(4):275–258.
6. Chowdhury AD, Oda M, Markus AF, Kirita T, Choudhury CR. Herbal medicine induced Stevens-Johnson syndrome: a case report. *Int J Paediatr Dent*. 2004;14(3):204–207.
7. Mochitomi Y, Inoue A, Kawabata H, Ishida S, Kanzaki T. Stevens-Johnson syndrome caused by a health drink (Eberu) containing ophiopogonis tuber. *J Dermatol*. 1998;25(10):662–665.
8. Dega H, Laporte J-L, Francès C, Herson S, Chosidow O. Ginseng as a cause for Stevens-Johnson syndrome? *Lancet*. 1996;347:1344.
9. Davydov L, Stirling AL. Stevens-Johnson syndrome with *Ginkgo biloba*. *J Herbal Pharmacother*. 2001;1(3):65–69.
10. Yuste M, Sánchez-Estella J, Santos JC, et al. [Stevens-Johnson syndrome/toxic epidermal necrolysis treated with intravenous immunoglobulins]. *Actas Dermosifiliogr*. 2005;96(9):589–592. [Spanish].

2010 Society of Hospital Medicine DOI 10.1002/jhm.639
View this article online at wileyonlinelibrary.com.