Stevens-Johnson Syndrome Induced by Doxycycline

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Stevens-Johnson syndrome (SJS) is an acute mucocutaneous eruption nosologically related to erythema multiforme (EM) and toxic epidermal necrolysis (TEN). Medications are the most common triggering factors for SJS, with anticonvulsants, sulfonamides, penicillins, allopurinol, and nonsteroidal anti-inflammatory drugs (NSAIDs) most commonly implicated. SJS is very rarely associated with tetracyclines. We report a case of doxycycline-induced SJS in a 46-year-old man.

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Stevens-Johnson syndrome (SJS) is a potentially life-threatening mucocutaneous eruption clinically characterized by a diffuse distribution of targetoid lesions or purpuric macules.[1] Histologically, epidermal necrosis with a subepidermal split and variable inflammation is seen.[2] SJS affects females twice as often as males and can occur in both children and adults.[1,3,4] The etiology most commonly relates to medications, particularly anticonvulsants, sulfonamides, penicillins, allopurinol, nonsteroidal anti-inflammatory drugs (NSAIDs),[5-13] and, rarely, cephalosporin and ciprofloxacin.[14-15] We describe a case of SJS associated with doxycycline. This is the second case of doxycycline-associated SJS reported in the English language literature.[16]

Case Report

A 46-year-old man presented with a blistering eruption of 4 days' duration. Two weeks prior to the eruption, doxycycline hyclate 100 mg twice daily had been started for a dental infection. He took no other medications and had not taken doxycycline in the past. Four days prior to presentation, a pruritic tender eruption developed on his central chest and back, quickly progressing to affect most of his body, including his palms, soles, and oral mucosa. He described his discomfort as "lying in the sand with a bad sunburn." A drug reaction was suspected; doxycycline was discontinued the day after the eruption began, and his primary care physician prescribed prednisone 60 mg daily 3 days prior to presentation to us. His past medical history was remarkable only for occasional oral aphthous ulcers, most recently 1 to 2 weeks prior to this eruption. He reported arthralgia and decreased oral intake secondary to tender oral lesions. He denied fever, chills, or night sweats.

Physical examination revealed a well-nourished uncomfortable man. Widespread (>50% body surface area [BSA]) 1- to 3-cm, erythematous, dusky macules and atypical targetoid macules were present on the trunk (Figure 1), extremities, face, palms, and soles, with confluence on the central trunk. Many of the targetoid lesions were centrally vesicular, purpuric, and superficially eroded, though sheets of

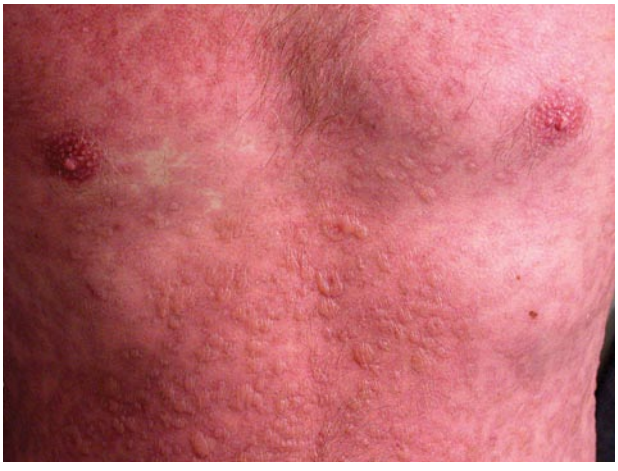

Figure 1. A 46-year-old man with Stevens-Johnson syndrome showing generalized erythema with edematous targetoid macules and formation of vesiculobullae on the trunk.

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epidermal necrosis were absent. Nikolsky sign was present, and skin detachment was estimated at 7% BSA. There were a few bullae and erosions of the buccal and labial mucosa, as well as soft and hard palate (Figure 2), with conjunctival erythema. There were a few erythematous macules on the base of the penis and scrotum, but urethral or perianal erythema was not present. A punch biopsy from the periphery of a typical vesicular lesion on the back showed interface dermatitis with full-thickness epidermal necrosis, and a mild superficial perivascular and interstitial inflammatory infiltrate, consistent with SJS (Figures 3 and 4). Direct immunofluorescence was negative. Laboratory investigations within reference range included liver function tests, complete blood count, electrolytes, blood urea nitrogen, creatinine, and chest radiography. Culture and direct fluorescent antibody testing for herpes simplex virus of oral lesions was negative.

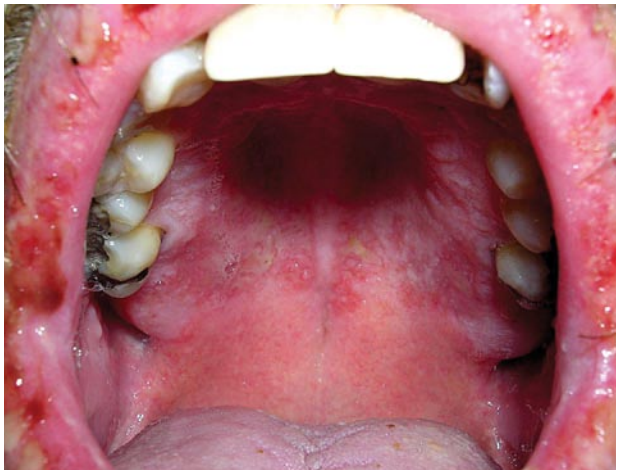

Figure 2. Erythema with erosion and superficial desquamation of the labial mucosa with hyperemia and punctate erosion on the palate.

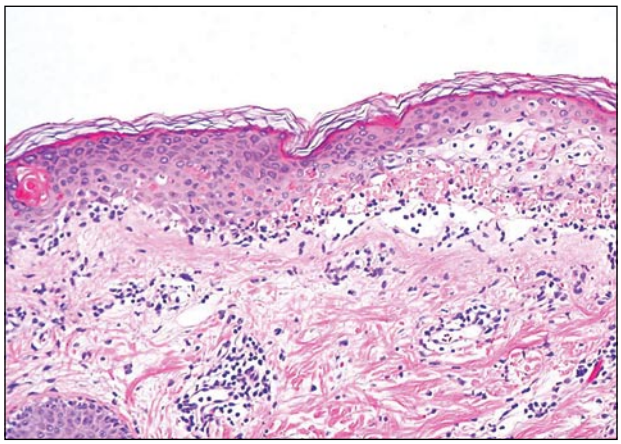

Figure 3. Punch biopsy specimen showing vacuolar interface dermatitis and focal keratinocyte necrosis progressing to subepidermal split with epidermal necrosis with hemorrhage, and a mild superficial perivascular and interstitial inflammatory infiltrate (H&E, original magnification ×40).

The patient was hospitalized and prescribed hydroxyzine hydrochloride 25 mg twice daily, mupirocin ointment for eroded areas, and continued prednisone, tapered to 40 mg once daily. During hospitalization, the patient was febrile to 39.2ºC, with blood and urine cultures negative for bacteria. At the time of discharge 5 days later, he was afebrile with an elevated white blood cell count attributed to the corticosteroid. The patient was much improved at the 2-week follow-up with fading of the eruption to postinflammatory hyperpigmentation. He remains free of recurrence one year later.

Comment

SJS is part of a continuum that includes erythema multiforme (EM) and toxic epidermal necrolysis (TEN). All 3 are characterized clinically by targetoid lesions and histologically by interface dermatitis and satellite necrosis of keratinocytes.[1] EM is a self-limited disorder that arises from a hypersensitivity response to certain infections (most commonly herpes simplex virus).[17] Lesions are diffuse, and frequently there is symmetrical extremity and facial involvement.[1,17] In contrast, the majority of SJS and TEN disorders are caused by drug reactions; lesions predominate the trunk, involve more than one mucosal site, and may show Nikolsky sign.[1] TEN is the most severe manifestation of this spectrum, with diffuse involvement, necrosis, and sloughing over 10% BSA and a significant risk of mortality.[1,17] Mortality of SJS and TEN is predictable by the severity-of-illness score for TEN (SCORTEN), using clinical and laboratory parameters (ie, age; heart rate; presence of malignancy; BSA involved; abnormalities in serum urea, bicarbonate, and glucose).[18] In this case, the 7-point SCORTEN analysis of these clinical parameters predicted a good prognosis with mortality risk of 12%.

SJS was first described in 1922,[19] and in 1950 it was proposed that EM be termed *EM minor* and SJS be termed *EM major* to reflect their similar pathologic process but differing severity.[20] EM major and SJS are now understood as distinct presentations. Morphologically, EM consists of typical or raised atypical targets on the extremities and face, while SJS consists of widespread purpuric macules or flat atypical targets favoring the trunk; in contrast to TEN, both have detachment at less than 10% BSA.[2,21,22] Cote et al[2] discussed the different histologic patterns between these entities, with EM major showing an interface dermatitis with lichenoid inflammation and SJS showing a predominantly necrotic pattern

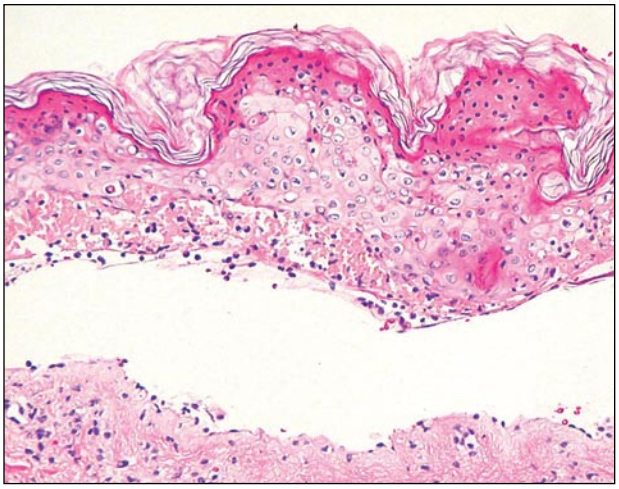

Figure 4. Punch biopsy specimen showing subepidermal split with full-thickness epidermal necrosis, hemorrhage, and a mild interstitial inflammatory infiltrate (H&E, original magnification ×100).

with major epidermal necrosis and minimal inflammatory infiltration. Recurrence of SJS is uncommon, but rechallenge in medication-induced cases results in more severe disease with shorter latency. HLA-A29, B12, B*1502, and DR7 haplotypes have been associated with SJS.[1,23]

Many drugs have been associated with SJS, especially anticonvulsants, sulfonamides, penicillins, allopurinol, and NSAIDs, and less commonly cephalosporin, tetracycline, quinolones, and imidazole antifungals.[5-13] Aside from drugs, physical factors such as UV light, x-ray exposure, and immune dysregulation may play a role.[1] The mechanism behind SJS lies in the cell-mediated cytotoxic immune reaction that destroys keratinocytes expressing foreign or drug-related antigens.[1,24]

Treatment of SJS includes hospitalization for supportive care. Systemic corticosteroids may be beneficial though controversial.[3] Recently, there has been great interest in the potential for treating SJS and TEN with intravenous immunoglobulin (IVIG), which inhibits apoptosis via an anti-Fas activity.[25] Studies of IVIG for SJS have reached conflicting conclusions. A retrospective study of 12 patients with SJS showed benefit of high-dose IVIG in blocking the progression of SJS and reducing the time to complete skin healing.[26] However, a prospective noncomparative study of 34 patients with SJS or TEN found no benefit of IVIG in reducing mortality.[25] In the present case, IVIG therapy was considered but was opted against as the patient's condition was responding to the corticosteroids that had been started locally. Early withdrawal of the offending medication was likely critical in his favorable course.[27]

Our patient represents a rare case of doxycycline-induced SJS. In our literature review, there was only one other reported case in the English language literature.[16] Another case has been reported in the French literature.[28] Awareness is essential of this rare but potentially life-threatening reaction to a medication commonly used in dermatology.

REFERENCES

1. Fritsch PO, Ruiz-Maldonado R. Erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. In: Fitzpatrick TB, Johnson RA, Wolff K, et al. *Color Atlas & Synopsis of Clinical Dermatology*. 6th ed. New York, NY: McGraw-Hill Professional; 2003:548-560.
2. Cote B, Wechsler J, Bastuji-Garin S, et al. Clinicopathologic correlation in erythema multiforme and Stevens-Johnson syndrome. *Arch Dermatol*. 1995;131:1268-1272.
3. Araujo OE, Flowers FP. Stevens-Johnson syndrome. *J Emerg Med*. 1984;2:129-135.
4. Levy M, Shear NH. *Mycoplasma pneumoniae* infections and Stevens-Johnson syndrome. report of eight cases and review of the literature. *Clin Pediatr*. 1991;30:42-49.
5. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. *N Engl J Med*. 1994;331:1272-1285.
6. Roujeau JC, Guillaume JC, Fabre JP, et al. Toxic epidermal necrolysis (Lyell syndrome). incidence and drug etiology in France, 1981-1985. *Arch Dermatol*. 1990;126:37-42.
7. Schopf E, Stuhmer A, Rzany B, et al. Toxic epidermal necrolysis and Stevens-Johnson syndrome. an epidemiologic study from West Germany. *Arch Dermatol*. 1991;127:839-842.
8. 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;126:43-47.
9. Bergoend H, Loffler A, Amar R, et al. Cutaneous reactions appearing during the mass prophylaxis of cerebrospinal meningitis with a long-delayed action sulfonamide (apropos of 997 cases)[in French]. *Ann Dermatol Syphiligr (Paris)*. 1968;95:481-490.
10. Heimbach DM, Engrav LH, Marvin JA, et al. Toxic epidermal necrolysis. a step forward in treatment. *JAMA*. 1987;257:2171-2175.
11. Rasmussen JE. Update on the Stevens-Johnson syndrome. *Cleve Clin J Med*. 1988;55:412-414.
12. Crosby SS, Murray KM, Marvin JA, et al. Management of Stevens-Johnson syndrome. *Clin Pharm*. 1986;5:682-689.
13. Bryant BG, Mathews BL. Stevens-Johnson syndrome. *Drug Intell Clin Pharm*. 1986;20:489-493.
14. Murray KM, Camp MS. Cephalexin-induced Stevens-Johnson syndrome. *Ann Pharmacother*. 1992;26:1230-1233.

15. Hallgren J, Tengvall-Linder M, Persson M, et al. Stevens-Johnson syndrome associated with ciprofloxacin: a review of adverse cutaneous events reported in Sweden as associated with this drug. *J Am Acad Dermatol*. 2003;49 (suppl 5):S267-S269.
16. Curley RK, Verbox JL. Stevens-Johnson syndrome due to tetracyclines—a case report (doxycycline) and review of the literature. *Clin Exp Dermatol*. 1987;12:124-125.
17. Murphy GF, Mihm MC Jr. The skin. In: Cotran RS, Kumar V, Collins T, et al, eds. *Robbins Pathologic Basis of Disease*. 6th ed. Philadelphia, Pa: WB Saunders Company; 1999:1170-1214.
18. Bastuji-Garin S, Fouchard N, Bertocchi M, et al. SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. *J Invest Dermatol*. 2000;115:149-153.
19. Stevens AM, Johnson FC. A new eruptive fever associated with stomatitis and ophthalmia. *Am J Dis Child*. 1922;24:526-533.
20. Thomas BA. The so-called Stevens-Johnson syndrome. *BMJ*. 1950;1:1393-1397.
21. Assier H, Bastuji-Garin S, Revuz J, et al. Erythema multiforme with mucous membrane involvement and Steven-Johnson syndrome are clinically different disorders with distinct causes. *Arch Dermatol*. 1995;131:539-543.
22. Bastuji-Garin S, Rzany B, Stern RS, et al. Clinical classification of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. *Arch Dermatol*. 1993;129:92-96.
23. Chung WH, Hung SI, Hong HS, et al. Medical genetics: a marker for Stevens-Johnson syndrome. *Nature*. 2004;428:486.
24. Correia O, Delgado L, Ramos JP, et al. Cutaneous T-cell recruitment in toxic epidermal necrolysis: further evidence of CD8+ lymphocyte involvement. *Arch Dermatol*. 1993;129:466-468.
25. Bachot N, Revuz J, Roujeau JC. Intravenous immunoglobulin treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis: a prospective noncomparative study showing no benefit on mortality or progression. *Arch Dermatol*. 2003;139:33-36.
26. Prins C, Vittorio C, Padilla RS, et al. Effect of high-dose intravenous immunoglobulin therapy in Stevens-Johnson syndrome: a retrospective, multicenter study. *Dermatology*. 2003;207:96-99.
27. 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.
28. Gallais V, Randrianjohanny A, Robineau M, et al. Stevens-Johnson syndrome caused by doxycycline [in French]. *Presse Med*. 1997;26:855.