A Middle-Aged Man with Newly Diagnosed HIV Infection and Rash

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CASE PRESENTATION

A 47-year-old man without any significant past medical history presented to the emergency department with a chief complaint of a skin rash of 12-days duration. He was recently diagnosed with HIV infection while hospitalized and treated for presumed pneumonia due to *Pneumocystis jiroveci*. Treatment of this infection consisted of trimethoprim-sulfamethoxazole and prednisone, a regimen which was continued as an outpatient. When seen in follow-up shortly after discharge, he was noted to have a rash over his trunk. Trimethoprim-sulfamethoxazole was discontinued and a regimen of clindamycin and primaquine was initiated. One day later he began to experience pain on the skin over his back as well as a progressive rash over the same area. He presented to the emergency department for further evaluation and management.

He denied fever, nausea, vomiting, alteration of hygiene practices, and changes in bowel or bladder habits. He had no pets, did not smoke tobacco or drink alcohol, and denied illicit drug use. No recent travel outside of New Orleans was reported. His past medical history was unremarkable, and he had no known medication allergies.

Vital signs in the emergency department revealed a blood pressure of 128/73 mmHg, a pulse of 68 beats per minute, a respiratory rate of 20 breaths per minute, and a temperature of 98.3°F. Purulent discharge and mild conjuctival injection were noted in both eyes. A diffuse maculopapular rash involving the face, neck, trunk, and all extremities (with sparing of the scalp, palms, and soles) was also present. Coalescent bullous lesions were observed on the ears, neck, abdominal wall, and lower back (Figure 1). Lateral detachment of the involved skin with manual pressure was appreciated, ie, Nikolsky sign. No oral, genital, or perianal lesion was seen. The abdominal, cardiac, pulmonary, and neurologic examinations were unremarkable.

CME INFORMATION

TARGET AUDIENCE

The May/June Clinical Case of the Month is intended for intended for general practitioners, medicine subspecialists including infectious disease, clinical pharmacology, allergy and immunology specialists, emergency medicine physicians, dermatologists, and pathologists.

EDUCATIONAL OBJECTIVES

The Clinical Case of the Month is a regular educational feature presented by the Louisiana State University Department of Medicine. Medical students, residents, postdoctoral fellows, and faculty collaborate in the preparation of these discussions. After reading this article, physicians should be better able to identify and to understand the pathophysiology, prognosis, clinical presentation, and treatment of toxic epidermal necrolysis. Estimated time to complete this activity is one hour.

CREDIT

The LSMS Educational and Research Foundation designates this educational activity for a maximum of one (1) *AMA PRA Category 1 Credit™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

DISCLOSURE

Drs. Njoku, Tate, Zadeh, Hauck, Chaudhry, Lo-Blais, Nesbitt, and Sanders have nothing to disclose.
Dr. Lopez discloses that he is a member of the *Journal* Board of Trustees and the *Journal* Editorial Board.

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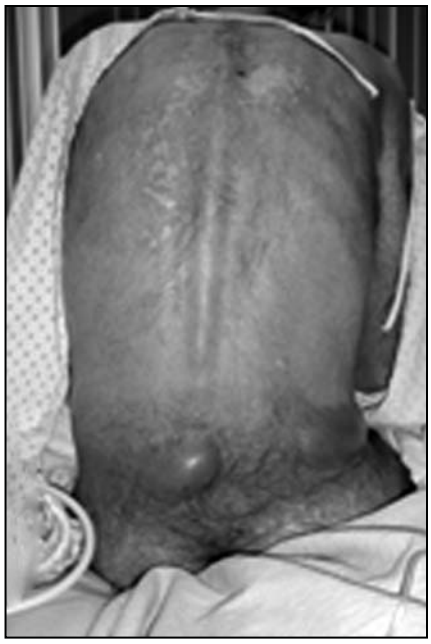

Figure 1. Erythematous rash with bullous lesions observed over the lower back.

Initial laboratory values revealed a total white blood cell count of 7.7 X 10^3/µL (normal range, 4.5-11.0) with a differential of 77% neutrophils and 2% eosinophils; hemoglobin of 11.9g/dL (normal range, 12-16); hematocrit of 43% (normal range, 35-46); blood urea nitrogen of 22 mg/dL (normal range, 7-25); serum creatinine of 0.7 mg/dL (normal range, 0.6-1.2); sodium of 132 mmol/L (normal range, 135-146); potassium of 4.7 mmol/L (normal range, 3.6-5.2); AST 40 U/L (normal range, <45); ALT of 56 U/L (normal range, <46); alkaline phosphatase of 56 U/L (normal range, 20-120); and albumin of 2.7 gm/dL (normal range, 3.4-5.0). Urinalysis revealed slight hematuria, and there was no serologic evidence of syphilis. The chest radiograph was without any reported abnormalities, and the CD4 count was 4/µL (normal range, 640-1175).

He was admitted to the intensive care unit with a presumed diagnosis of toxic epidermal necrolysis (TEN) secondary to trimethoprim-sulfamethoxazole. Toxic epidermal necrolysis was confirmed by skin biopsy (Figure 2), and intravenous immunoglobulin was administered. Clindamycin and primaquine were continued for treatment of pneumocystis pneumonia. No new skin lesions developed, and the rash resolved with subsequent skin desquamation and re-epithelialization.

DISCUSSION

Toxic epidermal necrolysis, also called Lyell syndrome, was first reported by Dr. Alan Lyell in 1956.[1] It is part of a spectrum of cutaneous drug eruptions which include Stevens Johnson syndrome (SJS), SJS/TEN overlap syndrome, and TEN. There are differentiated by the extent of involvement of the body surface, ie, <10%, 10-30%, and >30% in SJS, SJS/TEN overlap, and TEN, respectively.[2,3]

Epidemiology

Toxic epidermal necrolysis is a rare skin disorder with a reported incidence of 0.4-1.2 cases per million persons per year.[4] Women are affected more often than men by a ratio of 1.5:1. Therapeutic drug use is implicated in the majority of the reported cases.[5] The drugs typically involved include antibiotics, anticonvulsants, and nonsteroidal anti-inflammatory agents. Sulfonamides are the antibiotics which are most strongly associated, though all of the other classes of antibiotics have been implicated. Risk factors for development of TEN include advancing age, HIV infection, lymphoma, brain tumors, certain HLA haplotypes, and being 'slow acetylators' of drugs.[6-8] The overall mortality in TEN is 25-35%.

Clinical Features

Toxic epidermal necrolysis is an idiosyncratic drug reaction the features of which need to be differentiated from those in patients with staphylococcal scalded skin syndrome, acute generalized exanthematous pustulosis, generalized bullous fixed drug eruptions, and other bullous skin disorders (eg, pemphigoid). Symptoms typically start one to three weeks from the time of drug exposure. An initial prodrome of fever and flu-like symptoms usually precedes cutaneous manifestations by one to three days. Other early symptoms include skin tenderness, conjunctival itching, and dysuria.

Skin lesions typically start on the face and trunk and then spread over the body. The scalp is usually spared, though the palms and soles may be involved. The lesions are initially erythematous or dusky red ill-defined macules, which can be painful and pruritic. As full thickness necrosis occurs, the lesions develop a gray hue. When the epidermis

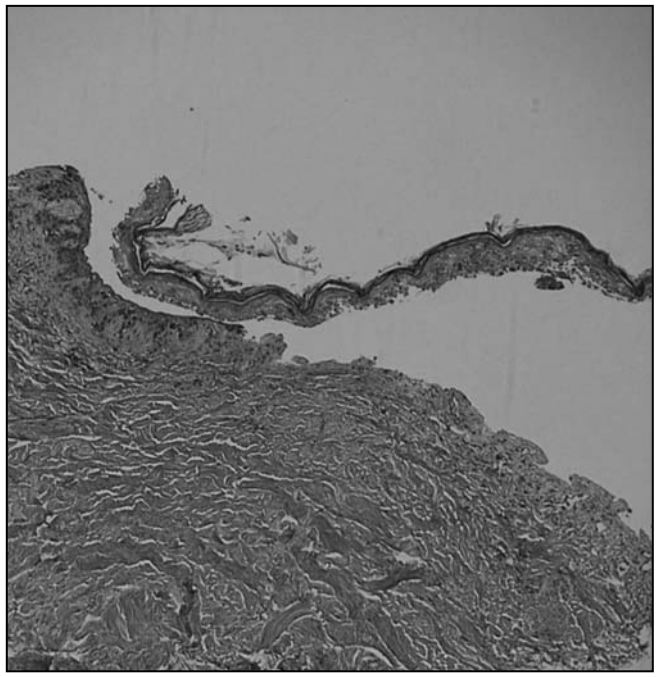

Figure 2. Histologic section of the lesion of toxic epidermal necrolysis demonstrates separation of the epidermis from the dermis. Hematoxylin and eosin stain.

separates from the dermis, fluid accumulates within this space leading to formation of vesicles that coalesce and become bullae. The bullae are typically flaccid, and the epidermis can be displaced laterally by slight thumb pressure (ie, Nikolsky sign). Blisters form within hours to a few days.

Mucosal involvement, including the conjunctivae, oral mucosa, respiratory epithelium, gastrointestinal tract, or urethra, is encountered in up to 90% of cases of TEN. The severity of this condition ranges from mild to severe including death. A scoring system for predicting mortality in TEN has been advocated by Bastuji-Garin et al and validated in a USA cohort, ie, the SCORTEN system.[9,10] It comprises seven clinical and laboratory parameters which are equally weighted. The parameters include age >40 years, presence of malignancy, initial surface area of epidermal detachment >10%, heart rate >120/minute, admission urea >10mmol/L (28mg/dl), serum glucose >14mmol/L (252mg/dl), and serum bicarbonate < 20mmol/L. The SCORTEN score ranges from 0 to 7 with a predicted mortality of 3.2% for a score of 0 to 1, and a predicted mortality greater than 90% for a score that is ≥ 5.[9,10]

Laboratory Abnormalities

Hematological abnormalities such as anemia and lymphopenia are common. Mild elevations of transaminases and serum creatinine are common and reflect the systemic nature of this reaction. However, more severe elevations, especially of creatinine, are associated with a poor prognosis.[11]

Pathogenesis

The pathologic mechanisms responsible for the skin lesions in TEN are only partially understood. The delay of one to three weeks from drug exposure to the onset of skin lesions reflects a possible period of sensitization. Symptoms occur earlier with re-exposure suggesting the existence of 'memory cells'. Cytotoxic T cells are seen early in the skin lesions, and several cytokines have been demonstrated in the blister-associated fluids, epidermis, and peripheral blood. These include tumor necrosis factor-alpha (TNF α), interleukin 6, interleukin 18, Fas ligand, soluble Fas ligand, and interferon gamma. The particular sequence of activation and actions of these cytokines is unclear, but the final pathway for epidermal necrolysis appears to be extensive apoptosis of keratinocytes. Several explanations have been proposed though none completely explains this pathologic mechanism.

Tumor necrosis factor-alpha has both anti-apoptotic and pro-apoptotic effects. It is unclear which of these predominate in TEN. However the increased mortality in patients given thalidomide, an anti-TNF agent, suggests that the anti-apoptotic effects of TNF-α might be beneficial in TEN.[12] Fas ligand binds to Fas receptors on keratinocytes to induce apoptosis, perhaps representing the final pathway in epidermal necrolysis. Perforin and granzyme B, which are found in high concentrations in blister fluids and peripheral mononuclear cells, induce keratinocyte death via non-apoptotic pathways. These pathways may ultimately represent therapeutic targets in TEN.

Histologically there is evidence of epidermolysis with mononuclear cell infiltration of the epidermis and epidermo-dermal junction. There is minimal cellular infiltrate in the dermis which has been described as 'dermal silence', a feature which distinguishes TEN histologically from other bullous diseases.[13]

Treatment

General: Optimal management of TEN includes early diagnosis, prompt discontinuation of suspected offending drugs, aggressive supportive care in a specialized unit, and specific therapies targeting the proposed pathogenic mechanisms. The low incidence of TEN precludes large prospective studies of different therapeutic options. The prompt discontinuation of any offending drug has been validated by case reports. It appears that the positive effect is seen more often with drugs that have short elimination half-lives than with drugs with prolonged half-lives.[14] The evidence also suggests that patients managed in specialized treatment areas (ie, a burn unit) have better outcomes.[15, 16] Aggressive supportive care includes management of fluid and electrolyte imbalances (which can be severe depending on extent of skin involvement), nutritional support, and prompt diagnosis and management of infectious

complications, the leading cause of mortality in TEN. Aseptic handling and reverse-isolation are recommended. The areas of skin loss are managed with local sterile dressing with the denuded epithelium left in-situ. A small case series of patients treated with *Biobrane* dressing, a semisynthetic skin substitute, showed reduction in pain and early wound healing with limited scarring.[17, 18] It is important to avoid silver sulfadiazine ointment, an agent typically used in the care of burn wounds, if the lesions were precipitated by use of sulfonamides.

Specific Treatments: Extracorporeal blood purification allows for removal of the causative drug, toxins, and cytokines. Plasmapheresis has been studied in TEN and appears to have a net beneficial effect on mortality. Continuous venovenous hemofiltration has not been studied in TEN, but might be useful in severe cases when plasmapheresis is unavailable.[12]

Studies of treatment with systemic steroids have yielded mixed results with many revealing either a neutral effect or an increased morbidity and mortality. It is thought that corticosteroids increase protein catabolism and the risk of sepsis and also impair re-epithelialization. There are also reports of TEN developing in patients receiving corticosteroids for other indications.[5, 12]

Thalidomide is a potent TNF-α inhibitor which has been investigated for the treatment of TEN. The trial was stopped early because of increased mortality in the thalidomide treatment group. The poor outcome in this trial could have been due to the different effects of TNF-α in TEN described earlier.[19] Thalidomide is currently contraindicated in TEN.

Intravenous immunoglobulin contains antibodies against Fas ligand, one of the cytokines causing keratinocyte apoptosis. Of nine non-controlled studies of the use of intravenous immunoglobulins in TEN published so far, seven showed a tendency toward improved outcome, usually with a cumulative dose of $\geq$ 2g/kg.[20-23] Possible reasons for the different outcomes include differences in study methodologies, in doses of intravenous immunoglobulins, and in the time of enrollment into the studies from symptom onset. In addition, there is variation of anti-Fas ligand activity in intravenous immunoglobulins from different manufacturers and from different batches. Despite the uncertainty regarding efficacy, several investigators recommend the use of intravenous immunoglobulins in TEN.[24]

Cyclosporine is an anti-inflammatory agent with immunosuppressive and anti-apoptotic properties. Several case reports document a reduction in morbidity and mortality when cyclosporine was used to treat TEN. In addition, a case series of 11 patients with TEN reported a decrease in mortality with cyclosporine when compared to corticosteroids, cyclophosphamide, and placebo.[25] However, there was a trend towards more septic complications. A recent review article by Chave et al recommended the use of cyclosporine over intravenous immunoglobulin as first line management in TEN.[12]

SUMMARY

TEN is a rare cutaneous drug reaction associated with high morbidity and mortality. The underlying pathogenic mechanisms are poorly understood. Development of an effective treatment algorithm has been hampered by the low incidence of this disorder, incomplete knowledge of the mechanisms of epidermal death, and lack of large controlled trials to evaluate therapeutic interventions.

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CME QUESTIONS

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Choose the one answer that is most correct for each question.

1. All of the following are true concerning toxic epidermal necrolyis (TEN) except:
   a. Toxic epidermal necrolysis is a rare skin disorder with a reported incidence of 0.4-1.2 cases per million persons per year.
   b. The SCORTEN system uses specific laboratory and clinical data to predict mortality in TEN.
   c. Risk factors for the development of TEN include advancing age, HIV infection, lymphoma, brain tumors, certain HLA haplotypes, and being 'slow acetylators' of drugs.
   d. The overall mortality rate for TEN is <1%.

2. True/False:
   Mucosal involvement, including the conjunctivae, oral mucosa, respiratory epithelium, gastrointestinal tract or urethra, is encountered in only 10% of cases of TEN.

3. All of the following are true concerning TEN except:
   a. The drugs typically associated with TEN include antibiotics, anticonvulsants, and nonsteroidal anti-inflammatory agents.
   b. Symptoms typically start one to three weeks from the time of drug exposure.
   c. The pathologic mechanism responsible for the skin lesions in TEN is well-understood and is secondary to colonization with toxic strains of S. aureus.
   d. Optimal management of TEN includes early diagnosis, prompt discontinuation of suspected offending drugs, aggressive supportive care in a specialized unit, and specific therapies targeting the proposed pathogenic mechanisms.
   e. An initial prodrome of fever and flu-like symptoms usually precedes cutaneous manifestations by 1 to 3 days.

4. True/False:
   Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) differ in that SJS is a cutaneous drug eruption that involves <10% of the body surface area while TEN involves >30%.