RESIDENTS’ CLINIC

60-Year-Old Man With Rash

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A 60-year-old man presented with a rash that had developed during the previous 2 weeks. He had not experienced any symptoms of influenza or any other symptoms before the onset of the rash. The rash started on his scrotum and spread to his buttocks and then to his entire body. His face was spared, but he had pain inside his mouth. He first noticed a red, tender, pinpoint lesion on his scrotum, which became progressively larger with associated desquamation, pruritus, and worsening pain. An initial trial of topical hydrocortisone and then high-dose oral prednisone for 1 week was unsuccessful. He had no fevers or rigors. His medical history was unremarkable. Recent medications included corticosteroid preparations prescribed by his primary care physician. He had no known drug allergies. He drank alcohol occasionally but denied any recreational drug or tobacco use. He also denied any recent travel or unusual exposures.

On examination, the patient was afebrile; his blood pressure was 130/73 mm Hg and his heart rate was 123 beats/min. He appeared in distress secondary to pain. Fissures were visible over the angles of the mouth. The oral mucosa was dry, erythematous, and edematous, but no blisters, erosions, or ulcers were observed. Conjunctival erythema was present bilaterally without mucopurulent discharge. Skin examination revealed confluent, macular erythema with retraction and desquamation on most of the patient’s body surface area (Figure). The hands were edematous with satellite red macules and papules with central desquamation.

1. Which one of the following is the most likely diagnosis in this patient?
   a. Phototoxic eruption
   b. Staphylococcal scalded skin syndrome
   c. Stevens-Johnson syndrome (SJS)
   d. Toxic epidermal necrolysis (TEN)
   e. SJS/TEN overlap syndrome

Phototoxic eruptions are almost always drug induced. Drugs implicated include tetracyclines, quinolones, and amiodarone. The rash associated with phototoxic eruption is similar to exaggerated sunburn. Our patient’s history and physical examination findings argued against this diagnosis. Staphylococcal scalded skin syndrome usually occurs in children, as adults have specific antistaphylococcal antibodies to excrete the staphylococcal toxin through adequate renal clearance. Clinical manifestations of staphylococcal scalded skin include fatigue, fever, and a characteristic erythematous, pustular rash that is sandpaper-like and accentuated in flexor areas. It can be complicated by fragile and tense bullae that desquamate easily. Our patient’s skin examination findings were not suggestive of staphylococcal scalded skin syndrome. Stevens-Johnson syndrome is characterized by erythematous and/or purpuric macules and plaques. The skin lesions can progress to epidermal necrosis and sloughing. Mucosal membranes are usually affected, including ocular, oral, and genital areas. In SJS, skin sloughing is usually limited to about 10% of the total body surface area. Toxic epidermal necrolysis, also known as Lyell syndrome, is similar to SJS except that it involves greater than 30% of the skin. In our patient, typical skin lesions involved most of the body; on the basis of the percentage of body surface area involved, the most likely diagnosis was TEN. There is a continuum between SJS and TEN known as SJS/TEN overlap syndrome; such cases involve detachment of 10% to 30% of the skin. Our patient had a considerably higher total body surface area involved, making SJS/TEN overlap syndrome unlikely.

Laboratory studies yielded the following results (reference ranges provided parenthetically): hemoglobin, 15.6 g/dL (13.5-17.5 g/dL); leukocyte count, 15.0 × 10⁹/L (3.5-10.5 × 10⁹/L) with neutrophilia; platelet count, 298 × 10⁹/L (150-450 × 10⁹/L); sodium, 130 mEq/L (135-145 mEq/L); potassium, 4.3 mmol/L (3.6-4.8 mmol/L); chloride, 95 mEq/L (100-108 mEq/L); bicarbonate, 23 mEq/L (22-29 mEq/L); creatinine, 1.1 mg/dL (0.8-1.2 mg/dL); blood urea nitrogen, 17.7 mg/dL (8-24 mg/dL); glucose, 112 mg/dL (70-100 mg/dL); and plasma lactate, 3.56 mmol/L (0.6-2.3 mmol/L).

2. Which one of the following best explains this patient’s hyponatremia?
   a. Redistributive hyponatremia
   b. Syndrome of inappropriate antidiuretic hormone
   c. Hypovolemic hyponatremia
   d. Hypervolemic hyponatremia
   e. Medication-induced condition

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Redistributive hyponatremia (or pseudohyponatremia) can occur during severe hyperglycemia. The osmotic properties of glucose shift water from the intracellular to the extracellular compartment, with a resultant dilution in sodium. In our patient, plasma glucose levels were only mildly elevated. The syndrome of inappropriate antidiuretic hormone can result in euvolemic hyponatremia and can be caused by a variety of conditions, including any kind of central nervous system disturbance, tumors, and pulmonary disease. Our patient, however, was not euvolemic. Hypovolemic hyponatremia develops as both sodium and water are lost. As with burn trauma, the extensive skin damage in our patient resulted in substantial dehydration and hypovolemic hyponatremia. Hypervolemic hyponatremia occurs in conditions such as renal failure in which the kidneys are unable to excrete the sodium load or in cases of volume overload such as chronic heart failure or liver cirrhosis. Our patient did not have such features. Medications, including thiazide diuretics, acetazolamide, and some antipsychotic medications such as quetiapine, are an important and common cause of hyponatremia. Our patient denied the use of medications that could cause hyponatremia.

The patient received aggressive intravenous fluid hydration with normal saline and his vital signs normalized. Blood cultures, including fungal cultures, were drawn and multiple skin biopsies were performed. Biopsy specimens of the skin lesions revealed marked vacuolization of keratinocytes along the basal cell layer with acantholytic keratinocytes and a sparse infiltration of small lymphocytes along the dermal-epidermal junction, consistent with early TEN. Skin management included wet dressing changes to promote re-epithelization and strict measures to prevent nosocomial wound infections.

3. Which one of the following scoring systems is most appropriate for predicting our patient’s mortality rate?
   a. Rockall
   b. Apgar
   c. APACHE II
   d. TIMI
   e. SCORTEN

The Rockall score is sometimes used in acute upper gastrointestinal hemorrhage to establish and stratify the mortality risk by a numerical system.6 The Apgar score, which has 5 criteria, is used in the initial evaluation of newborns at 1 and 5 minutes after birth. The TIMI (Thrombolysis In Myocardial Infarction) score is used in acute coronary syndrome to predict mortality based on 7 independent variables.7 APACHE II (Acute Physiology and Chronic Health Evaluation II) predicts mortality in critically ill patients, taking into account age, diagnosis, prior treatment location, and other acute physiological and chronic health variables.8 A severity of illness score termed SCORTEN has been developed to predict mortality when evaluated in patients with TEN. The patient receives 1 point for each of the following variables: age older than 40 years, presence of malignancy, heart rate greater than 120 beats/min, initial epidermal detachment greater than 10% of the body surface area, serum urea level greater than 28 mg/dL, glucose level greater than 250 mg/dL, and bicarbonate level less than 20 mEq/L. Predicted mortality, which ranges from 3% to 90% depending on the SCORTEN score,9 was 35% in our patient. Although SCORTEN has recently been criticized for overestimating mortality,10 it provides a framework on which triage decisions can be based.

4. Which one of the following is most likely to complicate this patient’s disease and increase his risk of death?
   a. Immunodeficiency
   b. Dehydration
   c. Disease recurrence
   d. Sepsis
   e. Acute respiratory distress syndrome

Immunodeficiency (eg, infection with the human immunodeficiency virus) can predispose patients to SJS and TEN. However, to our knowledge, no instances of SJS/
TEN causing immunodeficiency have been reported in the literature. As with burn trauma, dehydration is an important complication of TEN; fluid resuscitation should be initiated immediately, with some patients requiring treatment in burn units. However, dehydration is not the most feared complication in TEN and does not necessarily lead to increased mortality. Disease recurrence generally occurs in patients re-exposed to the offending agent or to its related components. Some cross-reactions have been reported with related components of drugs, especially nonsteroidal anti-inflammatory drugs. Sepsis is the major cause of morbidity and mortality in patients with SJS and TEN, affecting 1.9% and 10.8% of patients, respectively. Acute respiratory distress syndrome can be a result of sepsis; however, it is not a direct complication of TEN.

After resuscitation with intravenous fluids for dehydration, our patient was deemed to be at increased risk of complications related to sepsis.

5. Which one of the following interventions is most appropriate in this patient?
   a. Prophylactic intravenous antibiotics
   b. Corticosteroids
   c. Thalidomide
   d. Plasmapheresis
   e. Ophthalmologic consultation and ocular care

Despite the increased risk of sepsis already discussed, prophylactic intravenous antibiotics are generally not used. However, it is important to anticipate infections and have a low threshold for treatment. Topical antibiotics, unlike systemic antibiotics, can be used. The use of corticosteroids in patients with TEN is controversial, and more studies are needed to assess the effect on morbidity and mortality. Thalidomide was once thought to be beneficial because of inhibition of tumor necrosis factor α. However, increased mortality was noted in a placebo-controlled study, and therefore thalidomide is contraindicated. Plasmapheresis has been shown to be effective in certain trials, but its use remains controversial and should not be routinely instituted. Conjunctival lesions ranging from hyperemia to corneal scarring that leads to blindness can occur as part of TEN. Ophthalmologic consultation and daily eye examinations should be routinely provided to any patient with SJS or TEN. In view of the conjunctival findings in our patient, the ophthalmology consulting service was asked to evaluate the patient. No ulcerations were detected, and carboxymethylcellulose eye drops were recommended with close follow-up.

The patient was closely observed and responded to supportive management. His condition improved without any complications, and he was discharged home 5 days later with daily wound care. An extensive and detailed history and review of systems in our patient revealed no clear culprit. Herbal supplements and over-the-counter nonsteroidal anti-inflammatory drugs are always a consideration in patients who otherwise do not take regular medications, but our patient denied the use of such agents. In the absence of a clear etiology, our patient’s presentation was attributed to idiopathic TEN.

DISCUSSION

Toxic epidermal necrolysis is an uncommon syndrome with an incidence estimated at 2 cases per million persons. Although rare, this clinical entity should be recognized early because of the potentially poor prognosis of patients with TEN. A detailed medication history is crucial when evaluating a patient with TEN because medications are the most common cause of SJS and TEN and many medications have been implicated. The most commonly implicated medications are antibiotics, including penicillins and sulfonamides, with the latter implicated more often than cephalosporins. Other common drugs include nonsteroidal anti-inflammatory drugs, analgesics, and antiepileptic medications. In one study, the incidence of medication-induced SJS was as high as 85%. Vaccination is a potential cause of TEN; however, a recent study showed that only a very small proportion of cases—6 cases out of more than 96,000 reported adverse events—could be attributed to vaccinations. Patients infected with human immunodeficiency virus who have a CD4 count of less than 200 cells/μL of blood routinely receive trimethoprim-sulfamethoxazole. Patients infected with human immunodeficiency virus who have a CD4 count of less than 200 cells/μL of blood routinely receive trimethoprim-sulfamethoxazole as prophylaxis for Pneumocystis jiroveci pneumonia. Toxic levels of hydroxyamine and metabolites and depleted systemic glutathione reserves have been proposed as an etiology of this adverse phenomenon.

The clinical features of TEN usually start with a proROME of fever and other influenza-like symptoms about 1 to 3 days before the development of the mucocutaneous lesions. Other clues to diagnosis include erythroderma, skin pain, palpable purpura, or swelling of the tongue. The skin lesions initially appear erythematous or purpuric and have a tendency to coalesce. As the lesions progress within days or, in severe cases, in just a few hours, they take on a more grayish hue. The necrotic epidermis then detaches from the dermis and fluid fills between the 2 layers, giving rise to blisters. The blisters break easily and have a positive Nikolsky sign (displacement of the blisters on lateral pressure). Toxic epidermal necrolysis is a clinical diagnosis and is confirmed by histology. Supporting laboratory abnormalities include anemia and neutropenia, the latter being as-
associated with a poorer prognosis.\textsuperscript{26} Mildly elevated liver enzymes are present in about 50% of all patients with TEN, and overt hepatitis occurs in approximately 10%.\textsuperscript{27} A high clinical suspicion for TEN is crucial because exposure to an offending agent can precede symptoms by 1 to 3 weeks.\textsuperscript{22} Classic pathologic findings include full-thickness epidermal necrosis with sparse inflammatory cell infiltrates. Characteristic histologic findings also include a dermal infiltrate constituted primarily of activated helper T lymphocytes, decreased numbers of Langerhans cells, and expression of the HLA-DR molecule on keratinocytes, which normally do not express this molecule.\textsuperscript{28} Characteristic \textit{satellitosis} (ie, the sparse infiltration of lymphocytes) has been described to develop at the dermoeipidermal junction, with lymphocytes clustered around dying basal keratinocytes.\textsuperscript{29}

The first step in the treatment of TEN is removal of the offending agent, which may decrease mortality.\textsuperscript{30} Supportive care is the mainstay of management and includes meticulous wound care, nutritional support, ocular care, and monitoring and treatment of any superinfections. Pulmonary complications may occur in addition to localized vaginal, urethral, and anal mucosal denudation. As such, monitoring for pulmonary failure and urologencologic complications is important. Most other treatment modalities have been ineffective or remain under investigation.\textsuperscript{5,11,14-19} Intravenous immunoglobulin has recently been proposed as a therapy for TEN. However, only limited data are available on the efficacy of intravenous immunoglobulin administration in patients with large desquamating skin lesions. Because intravenous immunoglobulin is extracted from a pool of at least 1000 donors, infection transmission is a risk. Currently, it remains unclear whether the benefits of intravenous immunoglobulin outweigh the risks.\textsuperscript{31}

\section*{REFERENCES}


