CASE PRESENTATION

A 54-year-old man with a past medical history of hypertension was hospitalized with intraventricular hemorrhage caused by an arteriovenous malformation and aneurysm of the posterior inferior cerebellar artery. A ventriculoperitoneal shunt was placed, and the patient was started on phenytoin for seizure prophylaxis on hospital day 12. The patient was discharged on hospital day 14 and was continued on phenytoin. Fifteen days after discharge, the patient presented to the emergency department with a complaint of lower facial swelling involving the perioral skin and lips that had developed 2 to 3 days ago. He was admitted to the hospital for suspected angioedema. During the hospitalization he developed fever, conjunctivitis, skin rash, and oral ulcers. Physical examination on the second day of admission revealed a temperature of 38.6°C. Eye examination showed bulbar conjunctivitis and false membrane (Figure 1). Oral examination revealed oral conjunctivitis and false membrane (Figure 1). Oral examination revealed oral ulcers and erosion of lips. Skin examination showed a macular skin rash over the trunk, back, and extremities, with epidermal detachment affecting less than 10% of the body surface area (Figures 2 and 3). Laboratory tests showed elevated liver enzymes: total bilirubin, 0.4 mg/dL (normal, 0.2–1.3 mg/dL); alkaline phosphatase, 160 U/L (normal, 33–133 U/L); alanine aminotransferase, 172 U/L (normal, 5–45 U/L); aspartate aminotransferase, 123 U/L (normal, 12–50 U/L). The patient’s leukocyte count was normal, and blood cultures were negative. A skin biopsy of the lesions revealed epidermal cell necrosis.
WHAT IS YOUR DIAGNOSIS?

(A) Toxic shock syndrome  
(B) Staphylococcal scalded skin syndrome (SSSS)  
(C) Stevens-Johnson syndrome (SJS)  
(D) Toxic epidermal necrolysis (TEN)

ANSWER

The correct answer is (C) SJS.

DISCUSSION

Toxic shock syndrome is caused by *Staphylococcus aureus* or group A streptococci. The skin manifestations in toxic shock syndrome are characterized by a diffuse, red macular rash resembling sunburn that also involves the palms and soles. Skin biopsy in this syndrome demonstrates bullae and blisters in the subepidermal layer with superficial and interstitial mixed cell infiltrates. SSSS is caused by an epidermolytic toxin produced by several strains of staphylococci. It is characterized by a macular erythematous rash that rapidly becomes sandpaper-like. The diagnosis of SSSS is verified by isolation of staphylococci from a site other than the blisters. The location of the cleavage plane on Tzanck preparation of a skin biopsy differentiates SSSS from TEN. In SSSS, the cleavage is in the granular layer of the dermis, while in TEN the cleavage is at the dermal-epidermal junction.

SJS and TEN are variants of the same process. Patients with SJS or TEN present with mucosal erosions, widespread erythematous cutaneous macules that often become confluent, epidermal detachment, and severe constitutional symptoms. Cases in which less than 10% of the epidermis is involved are labeled as SJS, those with 10% to 30% involvement are labeled as overlap SJS-TEN, and those with more than 30% involvement are labeled as TEN.

STEVENS-JOHNSON SYNDROME

Approximately 80% of cases of SJS-TEN are associated with medication use; the remaining cases are idiopathic. Common medications associated with this syndrome are sulphonamides, anticonvulsants, nonsteroidal anti-inflammatory drugs (NSAIDs), and allopurinol. A multicenter case-control study showed that the risk of developing SJS-TEN was increased with use of sulphonamide antibiotics (relative risk [RR], 172), carbamazepine (RR, 90), NSAIDs (RR, 72), phenytoin (RR, 53), and allopurinol (RR, 52). The annual incidence of SJS and TEN increases with age as there is increased exposure to medications with age.

The mortality rate in SJS is usually less than 5%, but mortality may be as high as 44% for TEN. A prognosis score (SCORTEN) recently has been elaborated and validated. This score is calculated by giving 1 point for each of 7 clinical variables evaluated during the first 24 hours: patient older than 40 years, malignancy, heart rate higher than 120 bpm, initial percentage of epidermal detachment greater than 10%, serum urea level greater than 28 mg/dL, serum glucose level greater than 252 mg/dL, and bicarbonate value below 20 mmol/L. The total number of points is used to predict mortality (0–1 point, 3.2% mortality; 2 points, 12.3%; 3 points, 35%; 4, 58.3%; ≥ 5, 90%).

The pathophysiology of SJS is not well understood. One hypothesis involves immunologic mechanisms and an interaction between reactive drug metabolites. Experiments have shown that drug triggers can activate keratinocyte production of CD95 (Fas), an apoptotic ligand; binding of this ligand to a receptor on the keratinocyte cell surface leads to programmed cell death.

Approach to Diagnosis

The clinical features of drug-induced SJS and TEN usually develop 1 to 3 weeks after initiation of therapy. SJS-TEN begins with fever and poorly defined macules that coalesce to form blisters and progress to epidermal detachment. In cases of severe epidermal detachment, Nikolsky's sign (ie, ready separation of the outer layer of the epidermis from the basal layer with sloughing of the skin produced by minor trauma) is present. Mucosal involvement is seen in 90% of patients. Common sites of mucosal involvement are the conjunctivae, the oral cavity, and genital mucosa. OCular involvement ranges from hyperemia to extensive false membrane formation with development of synchiae between the eyelids and conjunctiva.

The diagnosis of SJS-TEN is primarily clinical and is based on finding characteristic lesions on the skin and mucous membranes. The diagnosis can be confirmed by skin biopsy, which reveals full thickness epidermal necrosis. Most patients also have anemia and lymphopenia. Elevations in aminotransferases are present in approximately half of patients, and overt hepatitis occurs in 10% of patients.

Supportive Care

Patients with SJS-TEN are admitted to the hospital for management. General supportive care includes aggressive fluid and electrolyte management, nutritional support, pain control, and prevention of bacterial
superinfection. Skin care includes surgical débride-
ment and whirlpool therapy to remove necrotic epider-
mis, if needed. Topical antibacterial ointment or silver
sulfadiazine may be applied to débrided surfaces. Eye
care includes lubrication with artificial tears or lubricat-
ing ointment and daily examination by an ophthalmol-
ologist. Prophylactic antibiotics are not recommend-
ed. There are no specific guidelines regarding when to
transfer patients to the intensive care unit or to a burn
unit, but studies have shown that prompt referral re-
duces the risk of infection, mortality rate, and length of
hospitalization.15

**Therapeutic Options**

Corticosteroids and intravenous immunoglobulin
(IVIG) have been used to treat SJS and TEN. There are
some reports of benefit from treatment of SJS patients
with systemic corticosteroids. However, retrospective
studies have shown that short courses of corticosteroids
enhance morbidity. One study showed that IVIG can
inhibit Fas-Fas ligand-mediated apoptosis of epidermal
cells in SJS and TEN. Several studies have demonstrat-
ed decreased mortality with use of IVIG. The cur-
cently recommended dose of IVIG is 0.4 to 0.75 g/kg
for 4 days.

Other therapies that have been used to treat SJS and
TEN include plasmapheresis, cyclosporine, and thalido-
mide. Although some case reports have suggested a
benefit from plasmapheresis in patients with TEN, in an
open trial, plasma exchange produced no significant
difference in mortality, length of hospital stay, or time
to re-epithelialization. In a retrospective study involv-
ing 11 patients with TEN treated with cyclosporine and
6 patients treated with cyclophosphamide and cortico-
steroids, cyclosporine was safe and was associated with a
more rapid re-epithelialization rate and lower mortality
rate (0% versus 50%). A randomized trial found no
benefit of thalidomide 400 mg/d for 5 days in the treat-
ment of SJS-TEN. The trial was stopped early due to
excess mortality in the thalidomide group.

**CLINICAL COURSE OF CASE PATIENT**

After the diagnosis of SJS was made and confirmed
by skin biopsy, the patient initially was started on intra-
vavenous prednisone and benadryl. In addition, pheny-
toin was discontinued, and another drug was not started
for seizure prophylaxis. On the third day of hospitaliza-
tion, prednisone and benadryl were stopped and IVIG
1 g/kg for 3 days was initiated. The patient also received
supportive care for the oral ulcers, conjunctivitis, and
skin rash. He gradually improved, and his liver enzymes
returned to normal limits.

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