Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis in the Setting of Daptomycin Administration

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Abstract: We present a case of Stevens-Johnson syndrome/toxic epidermal necrolysis in a 71-year-old male patient who was treated with daptomycin for infection of a prosthetic shoulder joint. After total shoulder arthroplasty, he had developed symptoms concerning for infection and had a PICC line placed for antibiotic therapy. He developed fever, tachycardia, hypoxia, and a diffuse bodily rash involving the skin and mucous membranes. He was admitted to the hospital. Daptomycin was stopped and was treated symptomatically. He ultimately required transfer to the local burn unit–equipped facility and was able to be discharged after short convalescence.

Key Words: daptomycin, Stevens-Johnson syndrome, toxic epidermal necrolysis

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Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare mucocutaneous reactions with pathobiology that is not completely understood. Research thus far has implicated T cell–mediated and NK cell–mediated reactions in association with a wide variety of medications. These conditions exist on a spectrum, as they share common pathology.[1] Aside from stopping the offending agent, treatment is largely supportive and consists primarily of fluid resuscitation and coverage with empiric antibiotics against skin/soft tissue infections.[2] The major classes of medications found to be associated with SJS/TEN development are antibacterial sulfonamides, antiepileptics, and Oxicam-class nonsteroidal anti-inflammatory drugs.[3] In this case, a 71-year-old male patient treated with daptomycin for a joint prosthesis infection developed diffuse skin and mucous membrane blistering, later confirmed via biopsy to be SJS/TEN.

CASE

The patient is a 71-year-old man with a medical history of obesity, hyperlipidemia, sleep apnea, benign prostatic hyperplasia, paroxysmal atrial fibrillation, depression, cholelithiasis, and Fuchs' corneal dystrophy. His surgical history includes a right total shoulder arthroplasty, a right and left total knee arthroplasties, cervical fusion, and cholecystectomy. His medication regimen includes tamsulosin, losartan, duloxetine, atorvastatin, apixaban, and carvedilol.

He had a right total shoulder arthroplasty, which 6 months postprocedure required revision due to continual pain and functional limitations. Although not purulent, during revision, the surgeons noted that the interior of the shoulder demonstrated the beginnings of infection. Cultures and Gram stains were obtained. Although awaiting culture results, he was started on empiric antibiotic therapy consisting of doxycycline and cephalexin. Joint fluid and tissue cultures later grew *Cutibacterium acnes* and *Corynebacterium* species. A PICC line was implanted, and he was started on daptomycin, by an outside facility, for outpatient antibiotic therapy.

Approximately 4 weeks later, the patient presented to the ER with fever, chills, myalgia, and a sore throat. The symptoms had developed earlier the previous day. He denied any sick contacts. On physical examination, he was noted to have a fever of 104.1°F and tachycardia with irregular rhythm. He was ill-appearing and diaphoretic. Because of an initial concern for sepsis, fluid resuscitation was started, and blood cultures and imaging were obtained. A chest radiograph showed no acute process, and the surgical hardware appeared intact. A CT scan of the abdomen and pelvis likewise showed no acute process. He was admitted to the general medical floor, his daptomycin was held, and he was started on a broader-spectrum antibiotic regimen consisting of vancomycin and piperacillin/tazobactam. Because of the pandemic of coronavirus disease, COVID-19 testing was obtained and was negative.

After his first night on the general medical floor, he developed a flat, erythematous rash involving his abdomen and thighs. The rash was painful, and blanched when pressure was applied. He also developed diffuse swelling of the penis and testicles, along with erythema and blisters. The infectious disease service was consulted, and there were concerns for necrotizing fasciitis, which stopped his vancomycin and piperacillin/tazobactam, restarted his daptomycin, and started meropenem.

That evening, the patient acutely decompensated. Nursing staff noted abrupt mental status change, fever of 105°F, and an oxygen saturation of 88%. Ice packs were used for external cooling, Noninvasive ventilation was applied, and he was transferred to the intensive care unit for further management.

He was stabilized in the intensive care unit, and his mental status and vitals returned to baseline. His skin rash worsened and began to blister, covering his arms, legs, chest, back, genitals, and face (Figs. 1, 2). Involvement of his oral mucosa was noted, with his lips blistering and peeling, making it painful to eat or drink. His daptomycin was held. Objective results were not supportive of sepsis, including a normal white blood cell count, an unremarkable chest radiograph, and resolution of fever and hypoxia. Blood cultures obtained earlier showed no bacterial growth. These results, in conjunction with his worsening mucocutaneous rash, suggested a drug reaction. His meropenem was stopped, and he was monitored off antibiotics. Dermatology was consulted, and a skin biopsy was obtained, which confirmed SJS/TEN (Figs. 3–5).

The patient remained stable on the floor for another day and was transferred to another facility equipped with a burn unit. There, he continued to improve with supportive care measures. A viscous lidocaine-based mouthwash was used to help with oral pain and eating, and mupirocin ointment was applied to areas of desquamation on his skin for infection prevention. His case was

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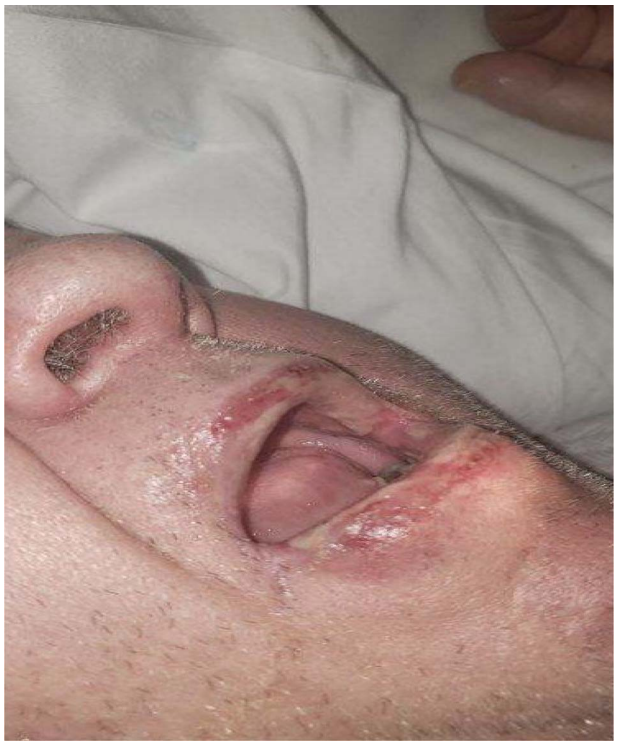

FIGURE 1. Desquamation of mucus membranes of oral mucosal.

classified as mild to moderate, so etanercept and/or intravenous immunoglobulins were not used. His skin lesions eventually improved, and he was able to ambulate and feed himself normally.

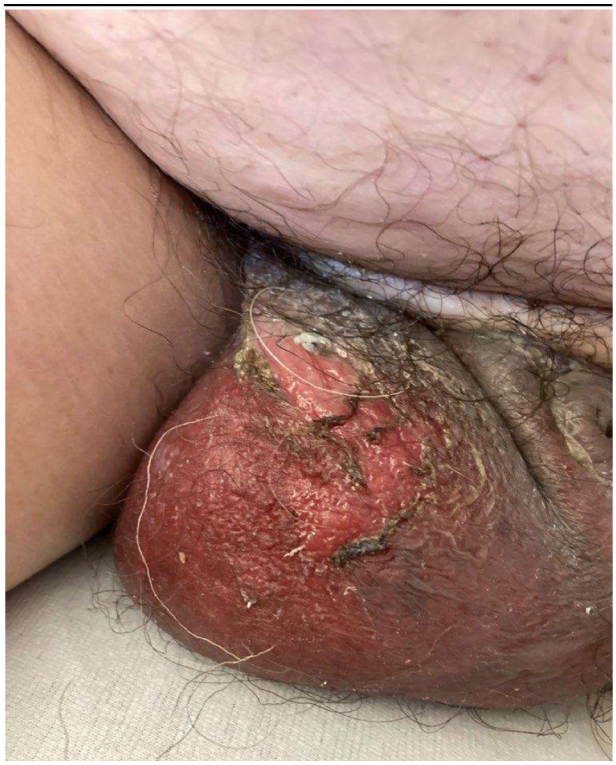

FIGURE 2. Desquamation of scrotum with surrounding erythema.

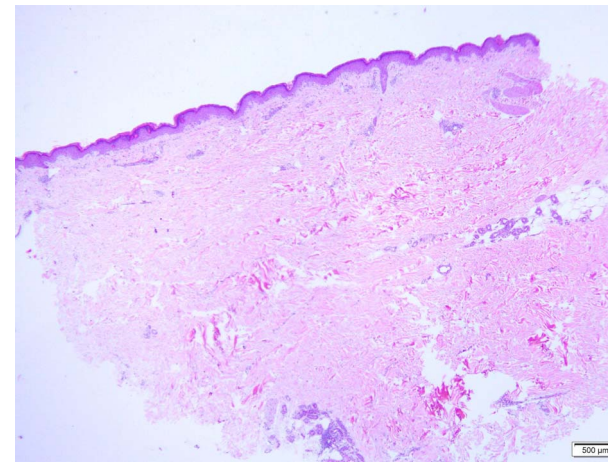

FIGURE 3. Punch biopsy (×20) hematoxylin-eosin stain. Hyperkeratosis, basal cell hydropic degeneration, and a mild dermal perivascular lymphocytic infiltrate.

He remained without signs of infection, and his PICC line was removed before discharge home.

DISCUSSION

Stevens-Johnson syndrome/TEN, as noted previously, shares association with a wide variety of drugs. The time course for skin lesions to develop is commonly 1 to 4 weeks after the initiation of the offending agent.[4] The timing of this patient's use of daptomycin implicated it in being the most likely causative medication. As with this patient, skin biopsy is required for a definitive diagnosis. Mortality rates can vary, and a validated scoring system known as the SCORTEN scale (SCORE of Toxic Epidermal Necrosis) was developed to help assess mortality rates for a particular patient.[5] In this case, the patient's lower SCORTEN scale (2) allowed more comfort in not using more aggressive resuscitative efforts, given a lower predicted mortality.

Daptomycin is not one of the "classic" pharmaceuticals associated with the development with SJS/TEN. A review of the literature revealed a paucity of evidence concerning association

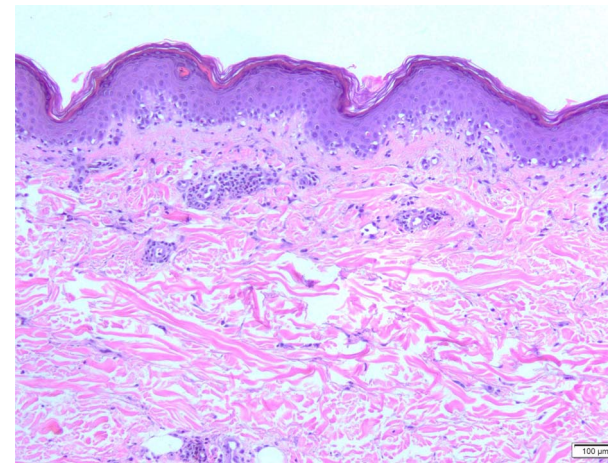

FIGURE 4. Hematoxylin-eosin (×100) basal cell layer vacuolization, occasional cytoid bodies, with a sparse perivascular lymphocytic infiltrate.

DIAGNOSIS:

SKIN, RIGHT UPPER THIGH, BIOPSY - INTERFACE DERMATITIS WITH NECROTIC KERATINOCYTES.
THE HISTOLOGIC FEATURES ARE CONSISTENT WITH ERYTHEMA MULTIFORME/STEVENS-JOHNSON SYNDROME
FINAL REPORT TO FOLLOW AFTER DERMATOPATHOLOGY REVIEW

Comment: The biopsy shows vacuolar alteration of the basal keratinocytes, necrotic keratinocytes at the interface, mild perivascular lymphocytic infiltration in the upper dermis and a patchy mild periadnexal lymphocytic infiltration. The histology is consistent with EM/SJS.

FIGURE 5. Pathology report of skin biopsy.

between these them. We believe this case to be an important possible association between daptomycin and the development of SJS/TEN.

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