Advanced Emergency Nursing Journal
Vol. 43, No. 3, pp. 194–197

DERMATOLOGY
DILEMMAS

Column Editor: Nicole Martinez, PhD, RN, FNP-BC, ENP-C, PHN

Sulfasalazine-Induced Toxic Epidermal Necrolysis
A Challenging Case During the COVID-19 Pandemic

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ABSTRACT
COVID-19 is a major health issue, and patients with underlying conditions are more susceptible to catastrophic outcomes. Toxic epidermal necrolysis (TEN) is a severe systemic disease caused by an immune system hypersensitive reaction. We present a case of TEN induced following sulfasalazine administration that later on complicated with COVID-19, deep vein thrombosis, pulmonary emboli, and eventually death. **Key words:** COVID-19, fatal coagulopathy, sulfasalazine, TEN

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Disclosure: *The authors report no conflicts of interest.*

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DOI: 10.1097/TME.0000000000000361

COVID-19 is a major health issue, and patients with underlying conditions are more susceptible to catastrophic outcomes (Food and Drug Administration, n.d.). Although this disease mainly involves the pulmonary system, it can also severely affect other organs, causing gastrointestinal distress, cardiovascular compromise, acute kidney injury, coagulopathies, cutaneous manifestations, and ultimately death from multiple-organ failure (Yi, Lagniton, Ye, Li, & Xu, 2020). Thrombotic complications and coagulopathy frequently occur in COVID-19, with their distinct characteristics seen with bacterial sepsis-induced coagulopathy (Iba et al., 2020).

Toxic epidermal necrolysis (TEN) is a severe systemic disease caused by immune system hypersensitive reactions characterized by more than 30% sheet-like epidermal detachment of the body surface (Schwartz, McDonough, & Lee, 2013). Drug hypersensitivity is responsible for 85%–90% of cases of TEN (Schwartz et al., 2013). The main manifestations of TEN are mucocutaneous, but multiple organs, such as trachea, bronchi, lungs, and so on, are also involved. It is widely established that the prevalence of mortality of patients affected with TEN varies from 25% to 30%, therefore rendering TEN as one of the most critical dermatology emergencies (Schwartz et al., 2013). Here, we present a case of sulfasalazine-induced TEN that later complicated with COVID-19, deep vein thrombosis (DVT), pulmonary embolism (PE), and eventually death.

Case History/Examination

A 52-year-old woman was admitted to the hospital with suspected TEN. Her symptoms had begun 5 days earlier following 2 weeks of sulfasalazine therapy for rheumatoid arthritis (RA). Sulfasalazine was prescribed by her rheumatologist. Following development of general and cutaneous symptoms, she was hospitalized in the intensive care unit (ICU) of a local hospital where no immediate access to dermatology consult was available. She was therefore transferred to our center to receive adequate dermatological services. Initial symptoms included fever and stinging eyes, followed by dusky red macular and flat atypical target lesions that had first appeared on her palms and sole, with rapid progression to more than 70% of her body surface (see Figure 1). Erythema and erosions of the buccal, ocular, and genital mucosae were present. Both Nikolsky and Asboe–Hansen signs were positive. Tense blisters were observed on her palms and soles (see Figure 2). The clinical diagnosis of TEN was made.

Histopathological findings revealed full-thickness epidermal necrosis and subepidermal bullae compatible with the diagnosis of TEN (see Figure 3). On Day 1, she presented with 38.3 °C fever and 98% oxygen saturation at room air. Laboratory tests revealed elevated levels of lactate dehydrogenase (648 units/L; normal: 140–280 units/L), C-reactive protein (52 mg/L; normal: less than 10 mg/L), and aspartate aminotransferase (59 units/L; normal: 10–40 units/L). Polymerized chain reaction (PCR) for COVID-19 was negative.

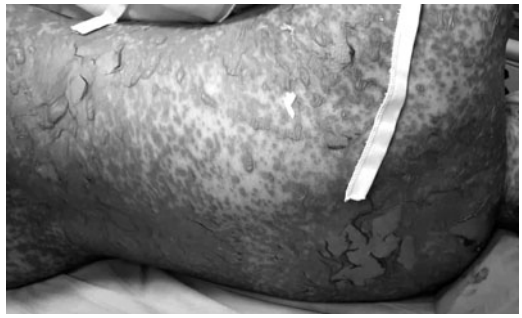

Figure 1. Cutaneous manifestation of toxic epidermal necrolysis: the tense blisters along with sheet-like epidermal detachment of the body.

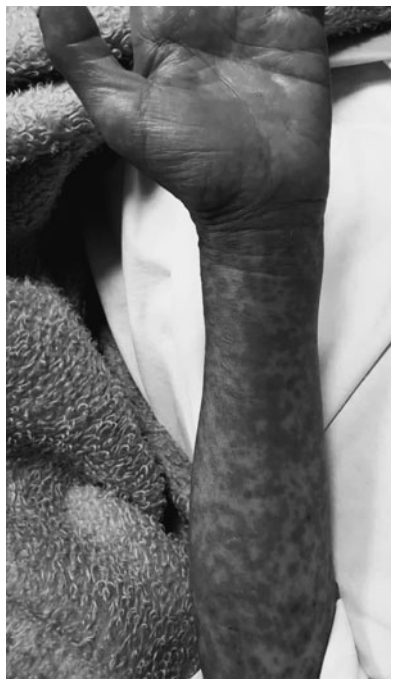

Figure 2. Cutaneous manifestation of toxic epidermal necrolysis: blisters on the palms.

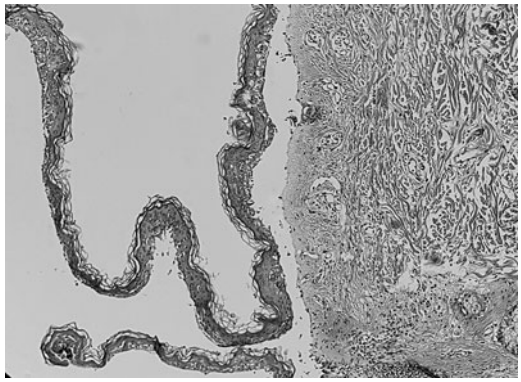

Figure 3. Histopathological features: blisters along with suprabasilar acantholysis of the skin.

After sepsis workup and an infectious disease expert's consultation, we started her on intravenous meropenem and vancomycin. For TEN, she received supportive care and oral cyclosporine 200 mg daily that led to an improvement of her skin condition within 3 days. On the fourth day of cyclosporine administration, re-epithelialization of lesions began. Despite marked improvement of skin lesions, her temperature rose to 38.8 °C after 5 days and she developed orthopnea. Spiral noncontrast chest computed tomographic (CT) scan was then performed, which revealed consolidation in the right lower lobe and posterior segment of the right upper lobe with air bronchogram sign, most likely due to bacterial pneumonia. Bilateral moderate-size pleural effusion was also present compatible with volume overload. We suspected bacterial infection was contracted during her previous stay at the ICU before the admission in our center. The antibiotics were then changed to ceftazidime and colistin according to the antibiogram of sputum culture. Cyclosporine was discontinued after 10 days.

On the 10th day of admission, her skin showed marked improvement but she developed productive cough and exacerbation of dyspnea. The follow-up CT scan showed bilateral peripheral and peribronchovascular ground glass opacity and interlobular septal thickening (acute crazy paving pattern) predominantly in lower lobes due to COVID-19 infection. Further PCR was positive for COVID-19 at Day 10 of her admission.

She was immediately transferred to the COVID-19 special ward where she received dexamethasone 6 mg daily and subcutaneous interferon beta-1a for 5 days. After 17 days of continuous care in the COVID-19 ward, she showed marked improvement and discharged to home quarantine after 27 days of total hospitalization. Unfortunately, she died of DVT and PE 1 month later.

DISCUSSION

Toxic epidermal necrolysis is a drug-induced mucocutaneous disease that results from keratinocyte cell death and dermal–epidermal and mucus membrane detachment, leading to the scalded appearance of the skin. The course of the disease is unpredictable, and the skin lesions may initially appear as benign dermatosis with a rapid progression to the skin detachment. It is shown that women, immunocompromised patients, and Asians with human leukocyte antigen (HLA) alleles are more likely to be affected (Bolognia, Schaffer, Cerroni, & Callen, 2018). Because of the loss of barrier function of the skin, this condition renders affected individuals more susceptible to contract infections such as COVID-19.

The COVID-19 pandemic has affected the treatment strategy of patients with RA whose infectious risk is increased compared with the general population (Favalli et al., 2020). Sulfasalazine is an effective and safe treatment option with significant benefit on the disease activity of patients with RA (Suarez-Almazor, Belseck, Shea, Wells, & Tugwell, 2000). However, the absolute risk of Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) in new users of 5-aminosalicylates, such as sulfasalazine, is estimated to be 1.9–4.3 per 100,000 (Frey et al., 2019). This risk must be taken into account before initiating this drug to patients during the current pandemic. This is particularly important for the emergency health care providers because TEN can progress rapidly and threaten the life of patients. On

the other hand, because of the limited protection against microorganisms, such as with COVID-19, these patients are more at risk of contracting infections. Therefore, fast and effective management of TEN patients by the emergency care providers is an important and lifesaving factor.

In addition, the initially negative PCR for COVID-19 in our patient could have been a false-negative result. There is a previous report of one symptomatic SJS/TEN case whose PCR turned positive following two negative results (Lagziel, Quiroga, Ramos, Hultman, & Asif, 2020). The false-negative PCR should be considered in patients with respiratory symptoms, especially in high-risk ones.

Finally, both bleeding and thrombotic complications are commonly reported following COVID-19 infection mainly due to the disseminated inflammation leading to hypercoagulability causing DVT or PE and eventually death (Al-Samkari et al., 2020). In managing COVID-19 patients, health care providers should screen for these complications and use anticoagulants when necessary. Although our patient was receiving rivaroxaban, she developed DVT and pneumatic emboli even after being discharged in a favorable condition. Thus, in managing patients with multiple respiratory comorbidities during the COVID-19 era, a multidisciplinary approach should be favoured.

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