

# Fulminating Course of Drug Reaction with Eosinophilia and Systemic Symptoms exacerbated by a Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis overlap

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**D**rug reaction with eosinophilia and systemic symptoms (DRESS) is an uncommon and severe adverse drug reaction with a mortality rate of up to 10%. It usually presents 2–6 weeks after the initiation of a new drug and may last despite drug discontinuation [1]. We believe ours is a rare case of progression of DRESS to histologically consistent Stevens-Johnson syndrome resulting in fatality.

## PATIENT DESCRIPTION

A 69 year old man with a history of chronic obstructive pulmonary disease (COPD), type 2 diabetes mellitus and multiple spinal surgeries was hospitalized with altered mental status and a diffuse erythematous rash. The rash appeared 1 week after a course of vancomycin (4 weeks) and doxycycline (1 week) for the treatment of a coagulase-negative staphylococcal spinal surgical site infection. It involved the trunk and arms and there was superficial desquamation on the face and arms.

On presentation, he was afebrile but required 4 L of oxygen administered by nasal cannula. Laboratory tests indicated systemic sepsis with leukocytosis of  $17 \times 10^3$  cells/ $\mu$ l, 53% eosinophils, platelets 21,000 cells/ $\mu$ l, and international normalized ratio

1.6. Initial creatinine, urea and liver enzyme levels were within normal limits. Blood and urine cultures were negative and a total body computed tomography scan did not reveal the source of the infection. Treatment for sepsis with intravenous vancomycin and piperacillin/tazobactam was initiated. During the first week of hospitalization the patient developed acute kidney injury with creatinine level rising to 3.1 mg/dl, as well as acute hepatitis. Antibiotic treatment was replaced by ciprofloxacin. A kidney biopsy showed acute interstitial nephritis with numerous eosinophils and foreign body giant cell granulomas, consistent with drug reaction. In view of worsening of the rash, ciprofloxacin was discontinued and treatment with high dose steroids was started. Skin biopsy at this time showed spongiotic and interface dermatitis with eosinophils, compatible with DRESS. The patient's mental status deteriorated progressively. Investigation for persistent tachycardia revealed elevated thyroid hormone levels consistent with thyroiditis. Transthoracic echocardiogram demonstrated heart failure with ejection fraction of 15–20% without wall motion abnormalities which could be explained by acute myocarditis. Tests for human herpes virus 6 were negative.

His general condition continued to deteriorate with new episodes of apnea necessitating transfer to the intensive care unit, where ceftaroline and ciprofloxacin treatment was begun due to concern of meningitis. Cervical puncture revealed 11 white blood cells/ $\mu$ m (predominantly polymorphs), and culture was positive for coagulase-negative staphylococci. The

antibiotic regimen was changed to linezolid. On the following day, new bullae and erosions appeared on the extremities [Figure 1A] accompanied by mucosal involvement and positive Nikolski sign. Repeat skin biopsy showed necrotic keratinocytes in all layers of the epidermis, compatible with early Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) [Figure 1B]. The patient subsequently developed *Staphylococcus aureus* bacteremia and died of septic shock.

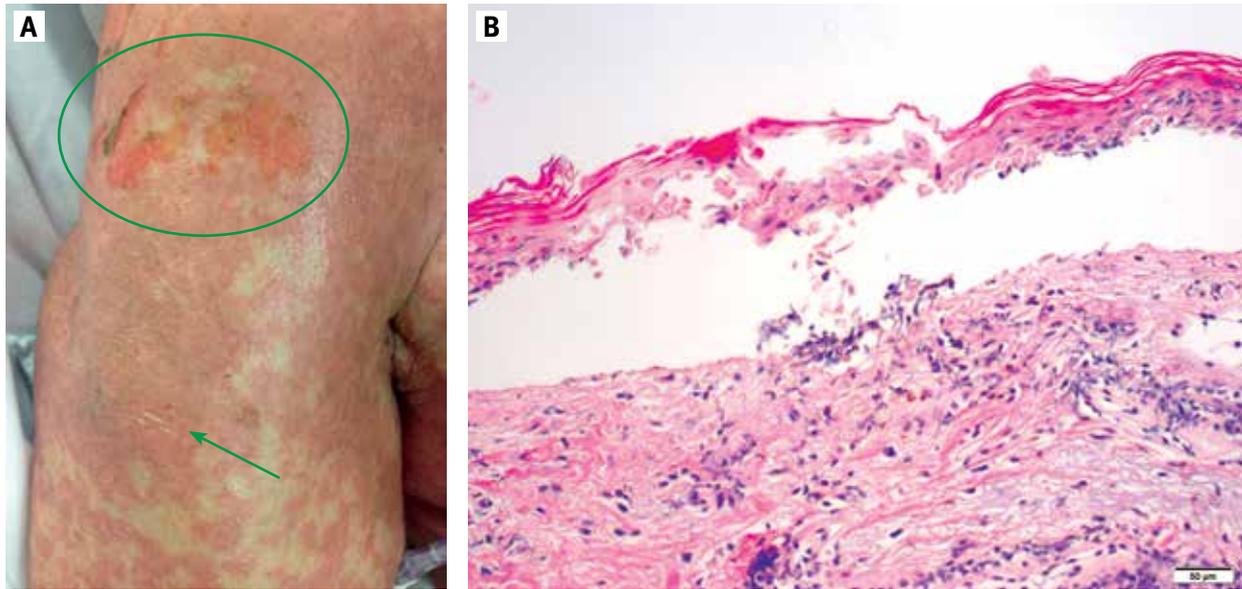
## COMMENT

The clinical criteria for diagnosis of DRESS include fever, rash, lymphadenopathy, hematologic abnormalities, systemic symptoms, internal organ involvement, and a history of causative drug administration. Visceral involvement may include pulmonary involvement, hepatitis, interstitial nephritis, myocarditis, pancreatitis, thyroiditis, meningitis, encephalitis, myositis and diarrhea [1].

Our patient was classified as a “definite case” of DRESS according to the RegiSCAR scoring system, with a calculated score of more than 5 points [1]. In addition, the patient developed most of the DRESS-associated systemic complications that are described in the recent literature while being treated with seven different antibiotic agents over a period of 1 month.

In a retrospective study of severe cutaneous adverse reactions, an overlap of SJS/TEN and DRESS was found in only 2 of 106 confirmed SJS/TEN-DRESS cases [2]. In addition to ours, there was only one

**Figure 1.** Patient’s clinical features suggesting the diagnosis of early SJS/TEN. **[A]** Right arm showing bullae (arrow) and erosions (encircled) superimposed on the original diffuse erythematous rash (credit: Dr. Eugene Balagula). **[B]** Skin biopsy from the patient’s right arm showing subepidermal blister with epidermal necrosis, with scattered necrotic keratinocytes at all layers of the epidermis, consistent with toxic epidermal necrolysis or Stevens-Johnson syndrome (hematoxylin & eosin staining).



reported case of histologically proven SJS/TEN-DRESS overlap [3]. It is unclear if the development of SJS/TEN was related to an underlying initial insult or resulted from additional drugs to which this patient was exposed.

Although there are no guidelines for the treatment of DRESS, identifying and discontinuing the suspected causative agent is the mainstay of treatment. Systemic corticosteroids are also suggested for cases with severe organ involvement [4]. Empiric treatment with antibiotics or anti-inflammatory drugs should not be administered during the acute period of the disease as they may confuse or worsen the clinical picture of the patient due to an unexplained cross-reactivity between drugs [4,5].

The present case report highlights the complexity of treatment in DRESS patients with severe multi-organ involvement. Avoiding the introduction of new medications to DRESS patients and to patients in whom DRESS is suspected may prevent disease progression and fatality.

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**“When dictatorship is a fact, revolution becomes a right”**

Victor Hugo (1802-1885), French poet, novelist and dramatist. His best-known works are *Les Misérables* and *The Hunchback of Notre-Dame*. He was also a campaigner for social causes such as the abolition of capital punishment

**“We all should know that diversity makes for a rich tapestry, and we must understand that all the threads of the tapestry are equal in value no matter what their color”**

Maya Angelou (1928-2014), American poet, memoirist, and civil rights activist