Case Report

Vancomycin-Induced Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome Masquerading as Elusive Sepsis

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1. Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is seldom seen, distinct, and a potentially life-threatening drug-induced Type IV hypersensitivity reaction that is frequently associated with reactivation of latent HHV-6 infections [1]. Symptoms characteristically start between two and six weeks after starting the offending drug and include a morbilliform cutaneous rash involving greater than 50% of body surface area, fevers, lymphadenopathy, and frequently multiorgan involvement. Laboratory findings generally include leukocytosis with marked eosinophilia, increased serum alanine aminotransferase, and atypical lymphocytosis. The pathogenesis includes an expansion of activated CD4 and CD8 cells which is thought to contribute to a reactivation of herpesvirus infections in most, although not all, cases. Although the incidence is unknown, one prospective study estimated an annual incidence of 0.9/100,000 [2]. The most commonly implicated agents include allopurinol and the anticonvulsive medications lamotrigine, carbamazepine, and phenytoin. Sulfonamides such as vancomycin are rarely associated with DRESS syndrome. In this report, we present a unique case of vancomycin-induced DRESS syndrome manifesting as an elusive endocarditis for several weeks before ultimately developing into florid eosinophilia and systemic symptoms.

2. Case Report

A 37-year-old female with a medical history significant for intravenous drug abuse initially presented to the Emergency Department (ED) complaining of right upper extremity pain and swelling of over the past day. Suspecting superficial thrombophlebitis, she was discharged from the ED with a prescription for clindamycin. However, the patient subsequently returned to the ED two days later with worsening right upper extremity pain and swelling now associated with fever and chills.

Vital signs on admission were notable for temperature 38.1°C, blood pressure 152/90 mmHg, and heart rate 124 beats per minute. Physical exam revealed the right forearm
to be significantly swollen on the medial aspect, with the area notably erythematous and warm to touch. Laboratory data showed a leukocytosis of 14,300/µl predominantly neutrophilic. Chest X-ray showed bilateral airspace disease, and subsequent computed tomography (CT) chest revealed innumerable right pulmonary septic emboli. Transthoracic echocardiogram and transesophageal echocardiogram were negative for vegetation. Broad spectrum antibiotics were initiated pending blood culture data, which resulted by the second day as positive for methicillin resistant staphylococcus aureus (MRSA) bacteremia in 4 out of 4 bottles. The patient was then transitioned to vancomycin monotherapy for an extended time course.

Surveillance cultures done on the fourth day of hospitalization were negative. In the interval, the patient underwent multiple incision and drainage procedures of several abscesses on her right upper extremity, the largest of which measured 3 cm in diameter.

Despite appropriate antibiotic therapy, the patient was spiking intermittent fevers. Investigation with repeat CT scan of the chest revealed bilateral loculated empyema. The patient subsequently underwent bronchoscopy and eventually right video-assisted thoracic surgery (VATS) procedure that was converted to open left thoracotomy for evacuation of loculated empyema, decortication, and placement of chest tube. Pleural fluid cultures were positive for MRSA.

The patient remained persistently febrile, with workup not revealing an identifiable cause. Surveillance blood cultures remained negative. Repeat CT scan of the chest revealed new small filling defect in the left lower lobe segmental pulmonary artery; however, the right sided filling defects had resolved. CT scan of the abdomen was pursued searching for other causes of fever but was unremarkable.

On day 22 of vancomycin therapy, liver enzymes were noted to be uptrending, with aspartate aminotransferase peaking at 2,563 units/L, alanine aminotransferase peaking at 1,192 units/L, and alkaline phosphatase peaking at 1,076 units/L (Figure 1). Within two days, new leukocytosis was noted and continued to uptrend for the next few days. On day 25 of vancomycin therapy, a diffuse maculopapular rash erupted involving bilateral upper and lower extremities as well as the upper chest (Figures 2 and 3). At this time, suspecting vancomycin-induced DRESS syndrome, antibiotic therapy was switched to ceftaroline. By day 29, the eosinophil count began uptrending, with absolute eosinophil count noted at 600/µl on day 35 (Figure 4). She concurrently developed acute kidney injury with blood urea nitrogen peaking at 27 mg/dL and serum creatinine peaking at 1.4 mg/dL (baseline creatinine 0.6 mg/dL). Multiorgan system involvement was noted as hepatic and renal dysfunction was evident on laboratory workup, and the patient subsequently developed cardiopulmonary instability requiring management in the medical intensive care unit. The patient eventually improved.
which are dark, macular, irregularly shaped lesions on the trunk and face, can be preceded by a mild, nonspecific syndrome. Within days, the lesions progress to flaccid bullae due to dermal-epidermal detachment, which tend to necrotize exposing the dermis [5]. The extent of cutaneous involvement of this disease spectrum ranges from STS (<10% body surface area) and STS/TEN overlap (10-30% body surface area) to TEN (>30% body surface area) [5].

AGEP typically manifests sooner, often within 48 hours, after administration of various medications including sulfonamides, ketoconazole, fluconazole, terbinafine, and diltiazem. The rash typically consists of innumerable pustules with minimal mucous membrane involvement. Neutrophilia is prominent on blood work [6].

Hypereosinophilic syndromes can also present with cutaneous manifestations that have a wide array of lesions. The most frequently reported reactions in this context include pruritic maculo-papules, urticarial manifestations, and angioedema [7].

Drug reactions secondary to vancomycin span a wide spectrum. The most common reaction is Red Man syndrome, manifesting as facial flushing, pruritus, and an erythematous rash of the upper body. The presentation often resembles a hypersensitivity reaction, though the true mechanism remains unclear [8–10]. Treatment generally consists of decreasing the rate of infusion and administering antihistamine agents [11].

Dermatological hypersensitivity reactions may range from a simple skin rash to Linear IgA Bullous Dermatosis (LABD), in which IgA autoantibody formation can be triggered by vancomycin [12]. Other dermatologic conditions include exfoliative dermatitis, leukocytoclastic vasculitis, SJS, and TEN. In the more dangerous clinical contexts, vancomycin must be stopped.

Vancomycin has caused various other drug reactions to include nephrotoxicity, hematologic abnormalities such as immune thrombocytopenia, and drug fever [3, 13]. Anaphylaxis, although rare, has also been associated with vancomycin administration [3].

Two cases of DRESS have been associated with a cross reactivity between vancomycin and teicoplanin, although in the latter the reaction to teicoplanin appears to be doubtful as symptoms started mere three days after initiation of the drug [14, 15].

The case presented offers multiple unique perspectives. The patient initially presented with fever and chills and was found to have multiple septic emboli to lung along with bilateral loculated empyema. The hospital course appeared to resemble that of sepsis for which the source remained elusive, though the patient was managed for thrombophlebitis, loculated empyema, and septic emboli. Additionally, the rash manifested four days prior to the evolution of eosinophilia, liver dysfunction, and acute kidney injury. This sequence of events represents an atypical presentation of DRESS syndrome.

Once DRESS syndrome is suspected, a prompt withdrawal of any high-risk medications serves as the initial and most important step in management. Supportive measures such as fluids, nutrition, and electrolyte balance
are also important. Both high dose topical and systemic corticosteroid treatment have been described although no randomized trials exist to support their use. The decision to use topical or systemic steroids is usually based on the severity of the reaction. In most of the above described cases, systemic corticosteroids were used with success. Treatment with cyclosporine has only been described successfully in a few cases, although this remains a second line treatment to corticosteroids [16, 17].

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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