Encephalopathy of Unclear Etiology: A Diagnostic Dilemma

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ABSTRACT

Introduction: Drug reaction with eosinophilia and systemic symptoms (DRESS) is a potentially fatal condition caused by drug exposure resulting in hypersensitivity reaction with involvement of different organ systems.

Case Presentation: We present a case of a 65-year-old man with a recent history of right total knee arthroplasty complicated by wound infection on a regimen of vancomycin who was transferred to our hospital for further management of fever, rigors, altered mental status, acute hypoxic respiratory failure, acute kidney injury, and development of an erythematous rash.

Discussion: DRESS syndrome was considered definite in this patient according to the European Registry of Severe Cutaneous Adverse Reaction Criteria, also known as RegiSCAR. To our knowledge, metabolic encephalopathy associated with multiorgan dysfunction resulting from vancomycin-induced DRESS syndrome has not been reported.

Conclusion: A thorough analysis of recent medication history is essential for the prompt identification and management of this condition.

INTRODUCTION

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a potentially fatal drug-induced hypersensitivity reaction with a long latent period from exposure to disease manifestation.[1] The reported mortality ranges from 3% to 10%,[2] and its prevalence has been reported at 2.18 per 100,000 patients.[2,3] Patients exhibit dermatological symptoms, fever, hematological abnormalities, and internal organ involvement.[4-7] Common culprits include but are not limited to antiepileptic drugs, antibiotics, sulfonamides, and antiviral medications.[1-9] The pathophysiology of DRESS is not fully understood, but is believed to be due to genetic predisposition in individuals exposed to the offending agents.[1,5] Reactivation of human herpes viruses (HHV) and other viruses also have been implicated in disease pathogenesis.[1,5,10-12]

We present a case of a 65-year-old man who experienced multiorgan failure and metabolic encephalopathy after vancomycin treatment. A thorough medication review is warranted for patients exhibiting neurological symptoms, multiorgan failure, and rash for prompt identification and treatment of DRESS.

CASE REPORT

A 65-year-old man was transferred to our facility for management of altered mental status, fever, rigors, acute hypoxic respiratory failure, acute renal failure, and diffuse maculopapular rash. Past medical history included nonocclusive coronary artery disease, major depressive disorder treated with venlafaxine and trazodone, and recent right total knee arthroplasty 2 months prior to the index visit.

One month after his arthroplasty, the patient developed wound dehiscence and drainage managed by washout and an intravenous (IV) regimen of vancomycin prior to discharge. He presented to an outside facility a month after initiating vancomycin with altered mental status, fever, and malaise. Shortly after, he developed acute respiratory distress, and an initial chest x-ray revealed bilateral pulmonary edema (Figure 1). He was intubated and mechanically ventilated. Based on his recent surgical history, the care team suspected septic arthritis and added meropenem

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Figure 1. Chest X-ray Revealing Extensive Interstitial and Alveolar Pulmonary Edema

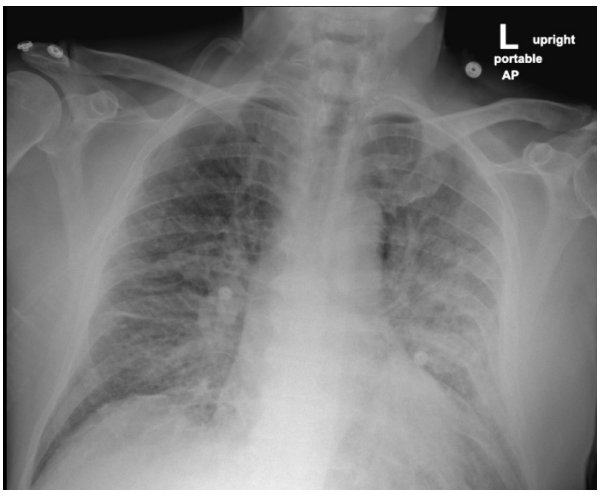
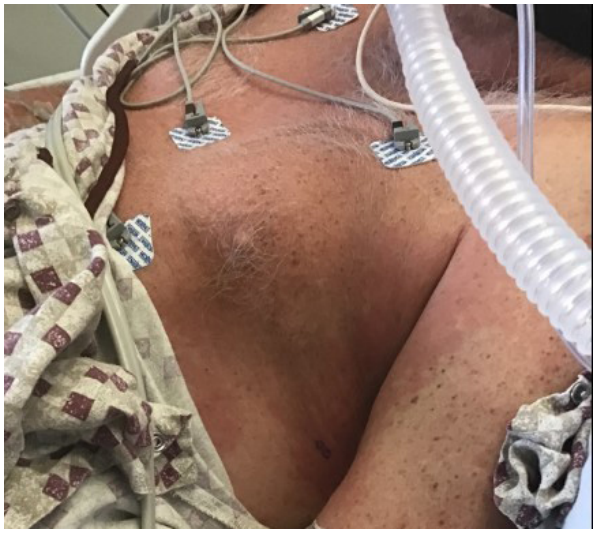


Figure 2. Photo of Index Patient's Chest and Left Arm



Erythematous, blanchable, poorly demarcated patches can be seen over the patient's chest and extremities with more pronounced erythema in the axilla. There are no areas of erosions, ulcerations, vesicles, or pustules seen.

to his preexisting vancomycin regimen. Despite being on broad-spectrum antibiotics, he continued to have altered mental status, fevers, and rigors. Serotonin syndrome was suspected due to long-term venlafaxine use and the presence of rigidity and clonus on physical examination. On his third day of hospitalization, the patient developed an erythematous rash with blanchable macules that coalesced into confluent patches involving his face, chest, and upper extremities, with more pronounced erythema in the axilla as well as desquamation involving the face, chest, and upper extremities. He had petechial macules and purpuric patches that were poorly demarcated on bilateral hands and feet, as well with surrounding significant pitting edema of the hands. There were no ulcerations, vesicles, or pustules on exam (Figure 2). This generalized rash initially was thought to be due to meropenem, which was discontinued and replaced with a regimen of piperacillin and tazobactam (Zosyn). He continued to be on vancomycin and was then transferred to our institution's medical intensive care unit.

At our facility, the patient received cyproheptadine for suspected serotonin syndrome, and his venlafaxine and trazodone were discontinued without resolution of symptoms. Laboratory analysis of blood and serum revealed elevated liver enzymes, creatinine, and procalcitonin levels as well as eosinophilia. His diffuse maculopapular rash persisted despite meropenem discontinuation and was thought to be "red man syndrome," which is a hypersensitivity reaction caused by degranulation of mast cells and basophils resulting in histamine release.[13] Thus, vancomycin was discontinued. However, he became agitated on his second day of hospitalization at our facility and continued to have decreased cognitive function.

A complete neurological workup on his third day of hospitalization included electroencephalogram and cerebrospinal fluid (CSF) analysis for infection and paraneoplastic syndromes. The electroencephalogram showed moderate diffuse slowing in a generalized fashion indicative of a generalized cerebral dysfunction and encephalopathy with no seizure activities observed. CSF analysis revealed pleocytosis with neutrophilic (72%) and eosinophilic (16%) predominance, as well as detectable numbers of red blood cells (Table 1); CSF cultures were negative for microbial infection. Serum and CSF paraneoplastic panels were also unremarkable, and there was no evidence of antinuclear antibodies and antineutrophil cytoplasmic antibodies. Magnetic resonance imaging of the brain was negative for encephalitis yet showed chronic microvascular changes. Arthrocentesis of the knee was negative for malignant

Table 1. Cerebrospinal Fluid Cell Count and Differential

Result	Value/Units	Normal/Units
Total nucleated cells	19/µL	05/µL
Red blood cells	7,100/µL	0–0/µL
Blast	0%	0–0%
Neutrophils	72%	0–6%
Lymphocytes	5%	40–80%
Monocytes	7%	15–45%
Eosinophils	16%	0–0%
Glucose	65 mg/dL	40–70 mg/dL
Total protein	37 mg/dL	15–45 mg/dL
Color	Colorless	
CSF-immunoglobulin	2.6 mg/dL	0.0–6.6 mg/dL
CSF-albumin	22.3 mg/dL	15.0–32.0 mg/dL
IgG/albumin	0.12	0.0–0.27

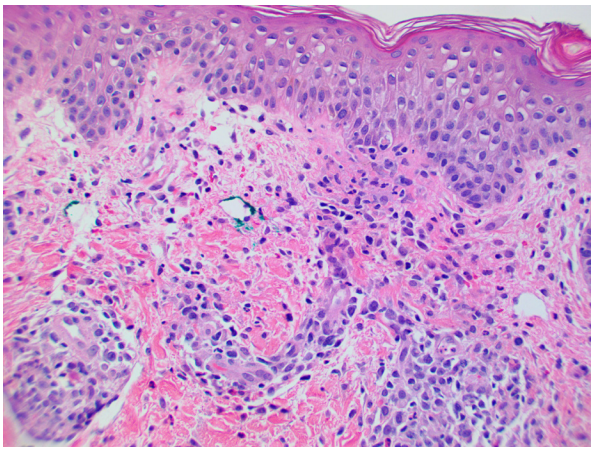
Abbreviation: CSF, cerebrospinal fluid

Table 2. European Registry of Severe Cutaneous Adverse Reaction (RegiSCAR) Patient Score

RegiSCAR Item		RegiSCAR Item Score if Present		RegiSCAR Item Score if Absent	RegiSCAR Item Score in Index Patient	Score in Index Patient
Fever ≥38.5° C		0		-1	Yes	0
Enlarged lymph nodes (>1 cm size, at least 2 sites)		1		0	No	0
Eosinophilia						
≥700 or ≥10%	≥1,500/μL ≥20%	1	2	0	Yes (3,400 cell/μL)	2
Atypical lymphocytes		1		0	No	0
Rash ≥50% of body surface area		1		0	Yes	1
Rash suggestive (≥2 of facial edema, purpura infiltration, desquamation)		1		0	Yes	1
Skin biopsy suggesting alternative diagnosis		-1		0	No	0
Disease duration >15 days		0		-2	Yes	0
Organ involvement						
1 organ	≥2 organs	1	2	0	Yes (≥ organ systems)	2
Investigation for alternative cause (blood cultures, antinuclear antibodies, serology for hepatitis viruses, mycoplasma, chlamydia) ≥3 done and negative		1		0	Yes	1
Total						7

*Total score <2: excluded; 2-3: possible; 4-5: probable; ≥6: definite.

Figure 3. Punch Biopsy From Left Lateral Chest With Hematoxylin and Eosin Staining Revealing Patchy Rocal Interface Dermatitis With Scattered Eosinophils and Neutrophils. (Magnification: 200x)



cells or infection. On day 4 of hospitalization, the patient was extubated to bilevel positive airway pressure, and dexmedetomidine was continued for his agitation. Since his symptoms were not consistent with serotonin syndrome, cyproheptadine was discontinued. In response to progressively worsening renal function and eventual acute renal failure secondary to acute tubular necrosis, he received continuous renal replacement therapy.

Due to the persistence of rash, multiorgan dysfunction, and eosinophilia, DRESS syndrome was suspected. A punch biopsy from the patient's lateral chest revealed patchy focal interface dermatitis with scattered eosinophils and neutrophils in the superficial to mid-dermis (Figure 3). His RegiSCAR (Registry of Severe Cutaneous Adverse Reaction) Criteria score was calculated (Table 2) and suggested a definite diagnosis of vancomycin-induced DRESS syndrome. Vancomycin was discontinued, and he was treated with high-dose IV methylprednisolone. This treatment was gradually tapered and replaced with a regimen of oral corticosteroids for 4 to 6 weeks to avoid relapse. With these measures, the patient's symptoms resolved completely, and follow-up neurological evaluation revealed a full recovery of his cognitive function and return of renal, pulmonary, and liver function back to baseline. He was discharged 27 days after hospital transfer.

DISCUSSION

DRESS syndrome is an uncommon but potentially life-threatening drug-induced hypersensitivity reaction.[1-9] Its clinical presentation is highly variable and, as a result, diagnosis requires a high index of clinical suspicion. DRESS is usually supported by a history of exposure to a high-risk medication within 2 to 8 weeks of systemic symptoms; appearance of a progressively morbilliform, erythematous, or exfoliative dermatitis; associated hematological abnormalities; and systemic organ involvement.[6,14] Delayed presentation after initiation of the offending medication is usually longer than most drug eruptions, which is 4 to 9 days for morbilliform drug eruptions and about 1 to 4 weeks for Stevens-Johnson syndrome/toxic epidermal necrolysis.[7,15]

Due to the atypical features of respiratory distress, altered sensorium, and multiple organ dysfunction before the rash appeared, DRESS syndrome initially was not considered. Given the patient's history of knee replacement with subsequent wound dehiscence, sepsis complicated with acute respiratory distress syndrome, and multiorgan dysfunction, metabolic or infectious encephalopathy was suspected. However, there was no identified infectious source. Our patient's rigidity, which initially raised concerns for serotonin syndrome, was considered to be secondary to his toxic metabolic encephalopathy secondary to multiorgan dysfunction. Persistence of these symptoms following several days of discontinuation of venlafaxine combined with cyprohep-

tadine administration and the development of a generalized skin rash made serotonin syndrome very unlikely.

Other inflammatory causes of disease also were considered, though such diagnoses were less consistent with his physical signs, symptoms, and negative results for autoimmune disease, infection, and paraneoplastic conditions. The patient also was evaluated for Stevens-Johnson syndrome and toxic epidermal necrolysis, which are associated with epidermal necrosis and mucosal involvement on at least 2 sites in 80% of cases.[14] However, eosinophilia is uncommon, and our patient's biopsy findings did not match the full-thickness epidermal necrosis generally seen with these conditions. Acute generalized exanthematous pustulosis, which usually starts <3 days after drug exposure, also did not fit the patient's clinical profile. Discontinuation of vancomycin corresponded to cognitive and functional improvements and supports our final diagnosis of DRESS syndrome.

CONCLUSION

A high index of clinical suspicion for DRESS is warranted for patients with a recent history of vancomycin who exhibit neurologic and pulmonary symptoms, multiorgan dysfunction, and no evidence of infectious or neoplastic disease with latent development of rash.

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