Amoxicillin-clavulanate induced DRESS syndrome masquerading as red man syndrome

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ABSTRACT

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a severe drug-induced hypersensitivity reaction carrying a mortality rate of up to 10%. We present a rare case of DRESS syndrome induced by amoxicillin-clavulanate, initially masquerading as red man syndrome. A 32-year-old male was admitted with flu-like symptoms and a maculopapular rash on the trunk and face that was exacerbated with vancomycin infusion, concerning for red man syndrome. He was receiving systemic antibiotics (vancomycin, ceftriaxone, and metronidazole) for infective endocarditis and previously took amoxicillin-clavulanate for a dental abscess. Despite the discontinuation of vancomycin, the exanthem continued to worsen, extending to involve >50% of his body surface area. Eosinophilia, hepatosplenomegaly, and acute kidney and liver injuries prompted consideration of DRESS syndrome. All antibiotics were discontinued, and systemic glucocorticoids were initiated. Punch biopsy revealed interface dermatitis with eosinophilic infiltrates; a high RegiSCAR score confirmed the diagnosis of DRESS. Amoxicillin-clavulanate was flagged as a severe allergy and deemed the culprit owing to the timing of exposure and personal/family history of hypersensitivity.

Keywords: Amoxicillin-clavulanate, DRESS syndrome, drug reaction, rash, red man syndrome, vancomycin

Case Report

A 32-year-old man with no significant past medical history underwent incision and drainage of a dental abscess after failing outpatient treatment with a 3-week course of oral 1 in 1000 to 1 in 10,000 drug exposures (predominantly to anti-convulsants) culminating in DRESS.[12-4] Owing to the latency period involved and high mortality rates, early suspicion is of paramount importance, particularly in the outpatient setting where DRESS initially manifests and should be considered as a potential diagnosis in symptomatic patients. We present here a rare case of DRESS syndrome induced by amoxicillin-clavulanate masquerading as red man syndrome.

Case Presentation

A 32-year-old man with no significant past medical history underwent incision and drainage of a dental abscess after failing outpatient treatment with a 3-week course of oral...
amoxicillin-clavulanate. He developed bradycardia during the procedure which resolved with atropine. A transthoracic echocardiogram (TTE) for evaluation of structural heart disease revealed a small mitral valve (MV) vegetation indicative of infective endocarditis. No microbes were isolated on blood or tissue cultures. Empiric intravenous (IV) antibiotic therapy with vancomycin, ceftriaxone, and metronidazole was instituted for culture-negative endocarditis. Though he tolerated the regimen well initially, 10 days later, he reported developing a pruritic, erythematous, maculopapular rash on his upper trunk, neck, and face. He reported worsening of the rash during vancomycin infusions. With concerns for red man syndrome, daptomycin was thus substituted for vancomycin, with initial stabilization of the exanthem allowing for discharge home to complete a course of IV antibiotics.

Two days later, he was admitted to our facility for evaluation of flu-like symptoms, reporting malaise, fevers, arthralgias, epigastric pain, and vomiting. Vital signs on admission showed T: 102.5°F, HR: 109 bpm, BP 114/69 mm Hg, RR: 20/min, and SpO₂: 100% on room air. Physical exam was remarkable for tender cervical and occipital lymphadenopathy (LAD), a 1–3-mm discrete maculopapular rash on the trunk and neck with negative Nikolski’s sign, several palatal petechiae, and a II/VI systolic murmur at the mitral area radiating to the axilla. Labs showed leukocytosis with eosinophilia (11.2%), lactic acidosis (peak of 4.0 mmol/L), acute kidney injury (AKI; Cr: 1.16 mg/dL; baseline value: 0.60 mg/dL), mild liver function test (LFT) derangements with AST: 63 U/L, ALT: 63 U/L, normal total bilirubin: 0.6 mg/dL, INR: 1.5, and PT: 17.2 s. Urinalysis, procalcitonin, respiratory PCR, EBV/CMV/HHV-6 testing, and blood cultures were unremarkable. Chest X-ray (CXR) was benign, and abdominal ultrasound showed hepatosplenomegaly. All antibiotics were held because of concern for DRESS syndrome given the patient’s eosinophilia, skin eruption, and visceral involvement. In 24 h, his rash progressed further to a diffuse coalescent eruption (follicular accentuation in places) extending to the upper and lower extremities; perioral swelling and honey-crusted scaling were observed [Figures 1–4]. His fevers (T max: 105.7°F) and transaminitis (peak AST U/L: 196; peak ALT: 514 U/L) worsened, suggestive of severe systemic involvement. With a RegiSCAR score of 6 and a punch biopsy revealing interface dermatitis with eosinophils, the diagnosis of DRESS was confirmed. Systemic (1.5 mg/kg/day of methylprednisolone) and topical glucocorticoids and antihistamines were rapidly initiated. The rash resolved with exfoliation and faded over the next 4 days; his acute liver injury and AKI also improved. A repeat TTE showed resolution of the MV vegetation, obviating the need for further antibiotic therapy. Later during the disease course, he divulged developing a mild skin rash while taking amoxicillin-clavulanate and reported amoxicillin allergies in his siblings as well. After being counseled to avoid beta-lactam antibiotics in the future, he was discharged home on as-needed antihistamines, topical glucocorticoids, and oral prednisone with outpatient follow-up and prolonged taper over 12 weeks to avoid a relapse.

**Discussion**

As illustrated in our patient, DRESS commonly presents with cutaneous (morbilliform eruption, facial edema, and mucous membrane involvement in nearly half of
patients) and systemic (fever, malaise, and tender LAD) symptoms, laboratory abnormalities (leukocytosis with eosinophilia, AST/ALT elevation, and HHV-6 reactivation) and manifestations of visceral involvement.[9] Antiepileptic agents, sulfa drugs, and antibiotics (particularly beta-lactams) are common culprits.[4,5]

Although testing in our patient was negative, reactivation of herpesviruses has been identified in a large proportion of patients, leading to the hypothesis that the pathogenesis of DRESS may involve viral reactivation stimulating the clonal expansion of T-cells with cross-reactivity to drugs; these cells subsequently attack viral antigens, resulting in disease manifestations.[6,7]

Interface dermatitis with lymphocytic or eosinophilic infiltrates is commonly observed on histology, as demonstrated by our case.[8] The RegiSCAR scoring system assists with diagnosing DRESS, commonly in a retrospective manner and at times even in the absence of a rash, eosinophilia, or systemic involvement.[9] We were able to definitively diagnose DRESS with a RegiSCAR score of 6 in our patient.

Ascertaining drug causality may be determined with patch tests or lymphocyte proliferation assays, but these are hampered by poor sensitivity. This, combined with the disease severity, made it prudent not to proceed with testing in the immediate aftermath of the acute phase of the illness in our patient.[9,10] Amoxicillin-clavulanate was identified as the precipitating medication in our case given the typical timeframe of exposure, in addition to personal and family history of prior allergic reactions to beta-lactams.

A low threshold for early evaluation is pivotal and would help identify cases so that appropriate management is instituted. Owing to the latency period, several cases may initially be observed in the outpatient setting. Thus, identification of the disease entity carries great significance for physicians practicing in family medicine and primary care settings. Immediate discontinuation of causative agents and initiation of systemic and topical glucocorticoids along with supportive care form the mainstay of treatment while severe cases may benefit from transfer to a burn unit.[12] IV immunoglobulins and immunosuppressive agents, for example, cyclosporine, cyclophosphamide, and rituximab, may be possible alternatives in patients who cannot take glucocorticoids. In our case, family members were cautioned about avoidance of causative drugs as well, with studies showing a degree of genetic predisposition.[13]

**Key Points**
- DRESS syndrome may rarely masquerade as red man syndrome
- Prolonged glucocorticoid taper helps prevent relapses in DRESS syndrome
- Herpesvirus reactivation is hypothesized to play a part in the pathogenesis
- It is important to distinguish DRESS from red man syndrome and other drug eruptions by maintaining a high index of suspicion and use of the RegiSCAR scoring system
- Family physicians and primary care providers play a key role in early diagnosis and referral/admission for further evaluation.

**Consent**
Informed consent was obtained from the patient for case publication.

**Declaration of patient consent**
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and anonymity cannot be guaranteed.

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**Conflicts of interest**
There are no conflicts of interest.

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