THE PATIENT

45-year-old man

SIGNS & SYMPTOMS

- Fever
- Generalized rash
- Recent history of calcaneal osteomyelitis

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THE CASE

A 45-year-old man was admitted to the hospital with a fever and generalized rash. For the previous 2 weeks, he had been treated at a skilled nursing facility with IV vancomycin and cefepime for left calcaneal osteomyelitis. He reported that the rash was pruritic and started 2 days prior to hospital admission.

His past medical history was significant for type 2 diabetes mellitus and polysubstance drug abuse. Medical and travel history were otherwise unremarkable. The patient was taking the following medications at the time of presentation: hydrocodone-acetaminophen, cyclobenzaprine, melatonin, and metformin.

Initial vital signs included a temperature of 102.9°F; respiratory rate, 22 breaths/min; heart rate, 97 beats/min; and blood pressure, 89/50 mm Hg. Physical exam was notable for left anterior cervical and axillary lymphadenopathy. The patient had no facial edema, but he did have a diffuse, morbilliform rash on his bilateral upper and lower extremities, encompassing about 54% of his body surface area (**FIGURE 1**).

Laboratory studies revealed a white blood cell count of 4.7/mcL, with 3.4% eosinophils and 10.9% monocytes; an erythrocyte sedimentation rate of 60 mm/h; and a C-reactive protein level of 1 mg/dL. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were both elevated (AST: 95 U/L [normal range, 8 - 48 U/L]; ALT: 115 U/L [normal range: 7 - 55 U/L]). A chest x-ray was obtained and showed new lung infiltrates (**FIGURE 2**).

Linezolid and meropenem were initiated for a presumed health care–associated pneumonia, and a sepsis work-up was initiated.

THE DIAGNOSIS

The patient's rash and pruritus worsened after meropenem was introduced. A hepatitis panel was nonreactive except for prior hepatitis A exposure. Ultrasound of the liver and spleen was normal. Investigation of pneumonia pathogens including *Legionella, Streptococcus, Mycoplasma,* and *Chlamydia psittaci* did not reveal any causative agents. A skin biopsy revealed perivascular neutrophilic dermatitis with dyskeratosis.

The patient was diagnosed with DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome based on his fever, worsening morbilliform rash, lymphadenopathy, and elevated liver transaminase levels. Although he did not have marked eosinophilia, atypical lymphocytes were present. Serologies for human herpesvirus (HHV), Epstein-Barr virus (EBV), and cytomegalovirus (CMV) were all unremarkable.

During discussions with an infectious disease specialist, it was concluded that the patient's DRESS syndrome was likely secondary to beta-lactam antibiotics. The patient had been receiving cefepime prior to hospitalization. Meropenem was discontinued and aztreonam was started, with continued linezolid. This patient did not have a reactivation of

FIGURE 1

Diffuse, morbilliform rash on the bilateral upper (A) and lower (B) extremities

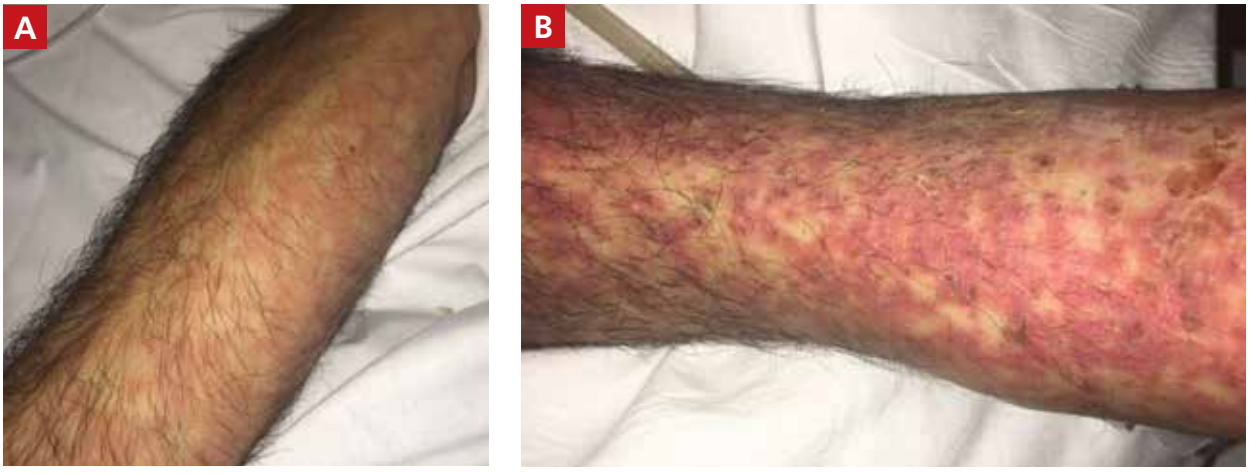

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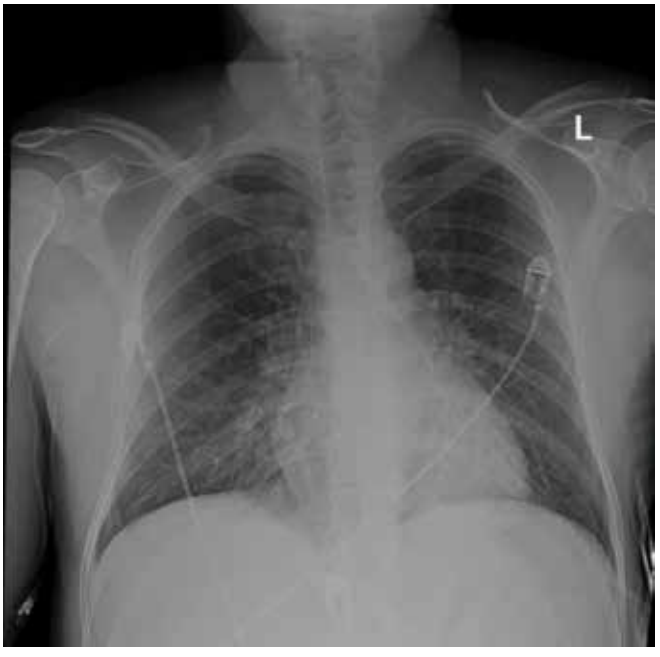
FIGURE 2

A chest x-ray showed new lung infiltrates



a herpesvirus (HHV-6, HHV-7, EBV, or CMV), which has been previously reported in cases of DRESS syndrome.

DISCUSSION

DRESS syndrome is a challenging diagnosis to make due to the multiplicity of presenting symptoms. Skin rash, lymphadenopathy, hepatic involvement, and hypereosinophilia are characteristic findings.[1] Accurate diagnosis reduces fatal disease outcomes, which are estimated to occur in 5%-10% of cases.[1,2]

Causative agents. DRESS syndrome typically occurs 2 to 6 weeks after the introduction of the causative agent, commonly an aromatic anticonvulsant or antibiotic.[3] The incidence of DRESS syndrome in patients using carbamazepine and phenytoin is estimated to be 1 to 5 per 10,000 patients. The incidence of DRESS syndrome in patients using antibiotics is unknown. Frequently, the inducing antibiotic is a beta-lactam, as in this case.[4,5]

The pathogenesis of DRESS syndrome is not well understood, although there appears to be an immune-mediated reaction that occurs in certain patients after viral reactivation, particularly with herpesviruses. *In vitro* studies have demonstrated that the culprit drug is able to induce viral reactivation leading to T-lymphocyte response and systemic inflammation, which occurs in multiple organs.[6,7] Reported long-term sequelae of DRESS syndrome include immune-mediated diseases such as thyroiditis and type 1 diabetes. In addition, it is hypothesized that there is a genetic predisposition involving human leukocyte antigens that increases the likelihood that individuals will develop DRESS syndrome.[5,8]

TABLE

RegiSCAR Score for DRESS

Total the scores from each of the clinical features listed in the table according to their presence, absence, or unknown status. Final scores < 2 are inconsistent with DRESS syndrome in most cases; scores of 2-3 indicate probable DRESS syndrome in most cases; and scores of > 5 are definitive for DRESS syndrome.

Features	No	Yes	Unknown
Fever (≥ 38.5°C)	–1	0	–1
Enlarged lymph nodes (≥ 2 sites, ≥ 1 cm)	0	1	0
Atypical lymphocytes	0	1	0
Eosinophilia 700-1499 mcL or 10%-19.9%	0	1	0
≥ 1500 mcL or ≥ 20%		2	
Skin rash extent > 50%	0	1	0
At least 2: Edema, infiltration, purpura, scaling	–1	1	0
Biopsy results suggestive of DRESS	–1	0	0
Internal organ involvement	0		0
1 organ		1	
≥ 2 organs		2	
Resolution in ≥ 15 d	–1	0	–1
≥ 3 biological investigations done to exclude alternative diagnoses	0	1	0

DRESS, drug reaction with eosinophilia and systemic symptoms; RegiSCAR, Registry of Severe Cutaneous Adverse Reactions.

Adapted from: Kardaun et al. *Br J Dermatol*. 2013.[9]

Skin rash, lymphadenopathy, hepatic involvement, and hypereosinophilia are characteristic findings of DRESS syndrome.

Diagnosis. The Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) was developed to assist in the diagnosis of DRESS syndrome.[9] Patients should be assessed for 11 criteria (outlined in the **TABLE**[9]), with points applied for the presence, absence, or unknown status of each. A total score of > 5 is consistent with definitive diagnosis of DRESS syndrome, while a score of > 2 indicates probable DRESS syndrome. Additionally, a skin biopsy may be contributory by revealing a dense infiltrate of eosinophils or lymphocytes in the papillary dermis, but this is not needed to make the diagnosis.[10,11]

Treatment is aimed at stopping the causative agent and starting moderate- to high-dose systemic corticosteroids (from 0.5 to 2 mg/kg/d). If symptoms continue to progress, cyclosporine can be used. N-acetylcysteine may also be beneficial due to its ability to neutralize drug metabolites that can stimulate T-cell response.[7] There has not been sufficient evidence to suggest that antiviral medication should be initiated.[1,7]

Our patient was treated with 2 mg/kg/d of prednisone, along with triamcinolone cream, diphenhydramine, and N-acetylcysteine. His rash improved dramatically during his hospital stay and at the subsequent 1-month follow-up was completely resolved.

THE TAKEAWAY

DRESS syndrome should be suspected in patients presenting with fever, rash, lymphadenopathy, pulmonary infiltrates, and liver involvement after initiation of drugs com-

monly associated with this syndrome. Our case reinforces previous clinical evidence that beta-lactam antibiotics are a common cause of DRESS syndrome; patients taking these medications should be closely monitored. Cross-reactions are frequent, and it is imperative that patients avoid related drugs to prevent recurrence. Although glucocorticoids are the mainstay of treatment, further studies are needed to assess the benefits of N-acetylcysteine. JFP

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