CASE REPORT

ONLINE **EXCLUSIVE**

THE PATIENT

32-year-old man

SIGNS & SYMPTOMS

– Fever
– Rash
– Leukopenia

Robert Gauer, MD; Collin Hu, DO; Lindsey Beaman, BS
Womack Army Medical Center (Dr. Gauer), Department of Research (Ms. Beaman), Fort Bragg, NC; 160th Special Operations Aviation Regiment, Fort Campbell, KY (Dr. Hu)

robertgauer@yahoo.com

The authors reported no potential conflict of interest relevant to this article.

THE CASE

A 32-year-old man was admitted to our hospital with fever, chills, malaise, leukopenia, and a rash. About 3 weeks earlier, he'd had oral maxillofacial surgery and started a 10-day course of prophylactic amoxicillin/clavulanic acid. Fifteen days after the surgery, he developed a fever (temperature, 103˚ F), chills, arthralgia, myalgia, cough, diarrhea, and malaise. He was seen by his physician, who obtained a chest x-ray showing a lingular infiltrate. The physician diagnosed influenza and pneumonia in this patient, and prescribed oseltamivir, azithromycin, and an additional course of amoxicillin/clavulanic acid.

Upon admission to the hospital, laboratory tests revealed a white blood cell count (WBC) of 3.1 k/mcL (normal: 3.2-10.8 k/mcL). The patient's physical examination was notable for lip edema, white mucous membrane plaques, submandibular and inguinal lymphadenopathy, and a morbilliform rash across his chest (**FIGURE 1**). Broad-spectrum antibiotics were initiated for presumed sepsis.

On hospital day (HD) 1, tests revealed a WBC count of 1.8 k/mcL, an erythrocyte sedimentation rate of 53 mm/hr (normal: 20-30 mm/hr for women, 15-20 mm/hr for men), and a C-reactive protein level of 6.7 mg/dL (normal: <0.5 mg/dL). A repeat chest x-ray and orofacial computerized tomography scan were normal.

By HD 3, all bacterial cultures were negative, but the patient was positive for human herpesvirus (HHV)-6 on viral cultures. His leukopenia persisted and he had elevated levels of alanine transaminase ranging from 40 to 73 U/L (normal: 6-43 U/L) and aspartate aminotransferase ranging from 66 to 108 U/L (normal range: 10-40 U/L), both downtrending during his hospitalization. He also had elevated levels of antinuclear antibodies (ANAs) and anti-Smith (Sm) antibody titers.

A posterior-auricular biopsy was consistent with lymphocytic perivasculitis. The rash continued to progress, involving his chest, abdomen, and face (**FIGURE 2**). Bacterial and viral cultures remained negative and on HD 4, broad-spectrum antibiotics were discontinued.

THE DIAGNOSIS

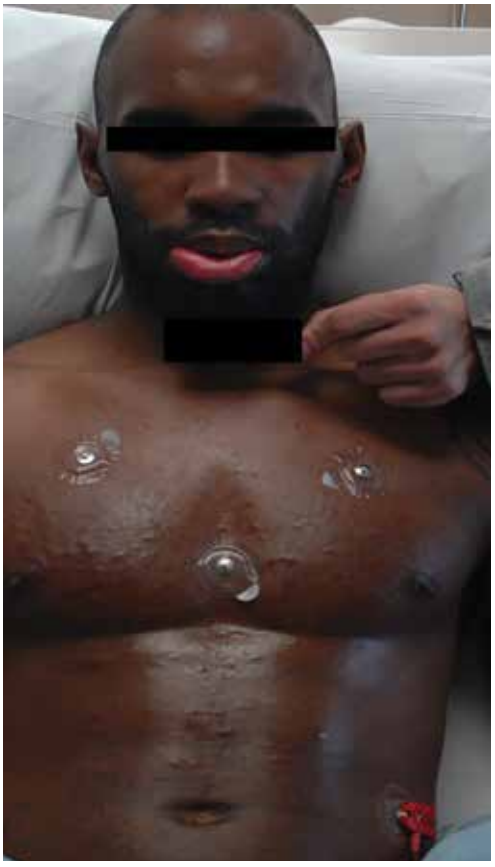
We diagnosed the patient with DRESS (drug reaction with eosinophilia and systemic symptoms) based on persistent fever, onset of cutaneous manifestations (facial edema and morbilliform eruption), lymphadenopathy, increased liver function tests, and recent exposure to an offending drug. The patient did not have eosinophilia; however, atypical lymphocytes were present on his peripheral smear.

DISCUSSION

DRESS is typically characterized by fever, rash, eosinophilia, atypical lymphocytes, lymphadenopathy, and organ involvement (primarily liver, but multiple organ systems can be af-

Patch testing and lymphocyte transformation tests can aid in the diagnosis of DRESS.

FIGURE 1
Morbilliform rash across chest



PHOTOS COURTESY OF: JOE HARLAN

FIGURE 2
Lip edema, rash on face

fected).[1] Patients with severe symptoms have renal involvement, anemia, respiratory and cardiac symptoms (chest pain, tachycardia, and myocarditis), and transaminase levels up to 5 times greater than normal.[1-3] Anticonvulsants and antibiotics are the most common offending classes among the medications that are associated with DRESS (**TABLE 1**).[2,4]

The reported incidence of DRESS is between one in 1000 and one in 10,000 drug exposures.[1] Due to the broad presentation and a lack of established diagnostic criteria associated with DRESS, this number may be even higher. DRESS has a 10% mortality rate,[1] and hepatic necrosis is the most common cause of death.[2]

Certain people may be more prone to DRESS. People with certain gene mutations that code for drug detoxification enzymes have shown a greater incidence of DRESS.[5] Viral reactivation, commonly of HHV-6, has also been shown to have an effect on the pathogenesis of DRESS. Additionally, genetic predisposition involving specific human leukocyte antigens (HLAs) makes certain people more prone to the development of DRESS (**TABLE 2**).[2,5]

Case reports have demonstrated a link between certain autoimmune syndromes and DRESS, specifically Grave's disease and type 1 diabetes mellitus.[2]

A unique finding of this case was the presence of elevated ANA and anti-Sm antibody titers at initial presentation, with spontaneous negative seroconversion 2 months later. Because of these 2 findings, as well as the patient's leukopenia and rash, he briefly met 4 of the 11 criteria set forth by the American College of Rheumatology for a diagnosis of systemic lupus erythematosus (SLE).[6] It is unclear whether the transiently elevated anti-Sm antibody titers were an acute phase reactant due to DRESS, a viral illness, or an evolving autoimmune process.

The false-positive rate for anti-Sm an-

TABLE 1

Medications associated with DRESS[2,4]

Drug category	Drug name
Anticonvulsants	Carbamazepine, gabapentin, lamotrigine, phenobarbital, phenytoin, valproic acid, zonisamide
Antidepressants	Bupropion, fluoxetine
Antihypertensives	Amlodipine, captopril
Antimicrobials	Amoxicillin, ampicillin, cefotaxime, ciprofloxacin, dapsone, ethambutol, isoniazid, linezolid, metronidazole, minocycline, piperacillin, pyrazinamide, quinine, rifampin, streptomycin, sulfasalazine, tazobactam, terbinafine, trimethoprim-sulfamethoxazole, vancomycin
Antivirals	Abacavir, nevirapine, zalcitabine
Biologic agents	Efalizumab, imatinib
Nonsteroidal anti-inflammatory drugs	Acetaminophen, celecoxib, diclofenac, ibuprofen
Proton pump inhibitors/histamine 2 blockers	Omeprazole, pantoprazole, ranitidine
Miscellaneous	Allopurinol, amiodarone, epoetin alfa, mexiletine

Adapted with permission from: Husain Z, Reddy BY, Schwartz RA. DRESS syndrome: Part I. Clinical perspectives. *J Am Acad Dermatol*. 2013;68:693.e1-e14.

tibodies in association with DRESS has not been previously reported.

MAKING THE DIAGNOSIS

Distinguishing DRESS from other life-threatening cutaneous drug reactions, particularly Stevens-Johnson syndrome and toxic epidermal necrolysis, can be difficult. Likewise, acute bacterial/viral infections, autoimmune syndromes, vasculitis, and hematologic diseases can mimic DRESS.[7] Exposure to an offending drug 2 to 6 weeks prior to the onset of symptoms is supportive of DRESS.

This scoring system can help. The RegiSCAR (Registry of Severe Cutaneous Adverse Reaction) has developed a scoring system to aid in the accurate diagnosis of DRESS.[1,8] The scoring consists of 8 categories: fever, eosinophilia, enlarged lymph nodes, atypical lymphocytes, skin involvement, organ involvement, time of resolution, and the evaluation of other potential causes.[1] Each category is graded a number from -1 (not supportive of DRESS) to 2 (highly supportive of DRESS) based on the patient's presentation. The total score grades potential cases as "no," "possible," "probable," or "definite."[1,8] In one review, cases classified as "probable" or "definite" by the RegiSCAR scoring system constituted 88% of the cases reported in the literature.[1]

Two tests that can also aid in the diagnosis of DRESS include patch testing (exposing the skin to a diluted version of the suspected offending drug and observing for a local reaction) and lymphocyte transformation tests. The latter are a better method of diagnosing drug-induced DRESS, with a sensitivity of 60% to 70%, and a specificity of 85%.[9] However, this testing is not readily available.

Once DRESS is diagnosed, the offending drug should be immediately discontinued. For mild cases, supportive treatment is recommended. For more severe cases, the use of corticosteroids tapered over several months is the treatment of choice.[10] Further studies are needed to determine the optimal type of corticosteroids, as well as the dose, route, and duration of therapy. Immunotherapy, plasmapheresis, and antivirals have been used with mixed results.[10,11]

Our patient was started on topical and systemic oral corticosteroids. Within 24 hours, his fever resolved and his rash improved. By HD 7, his laboratory values were normal and he was discharged.

CONTINUED

TABLE 2

HLA allele associations with DRESS[2,5]

Drug	HLA-allele
Abacavir	B*5701
Allopurinol	B*5801
Aminopenicillins	A2, Drw52
Aspirin	DRB1*1302, DQB1*0609
Carbamazepine	A*3101, A*11, B*1502
Gold sodium thiomalate	DR5
Iodine contrast media	DR , DR11
Lamotrigine	A*6801, B*5801
Nevirapine	B14, B*3505, Cw4, Cw8, DRB1*01
Paraphenylenediamine	DP
Phenytoin	B*1301, B*1502
Trichloroethylene	B*1301

Adapted with permission from: Alfirevic A, Pirmohamed M. Drug-induced hypersensitivity and the HLA complex. *Pharmaceuticals (Basel)*. 2011;4:69-90.

Long-term sequelae, such as Grave's disease and diabetes mellitus, have been reported following DRESS.

The patient was advised that in the future, he should avoid exposure to the penicillin class of medication.

THE TAKEAWAY

The presence of rash, fever, lymphadenopathy, eosinophilia, atypical lymphocytes, liver involvement, and HHV-6 reactivation in the absence of sepsis should raise suspicion for DRESS. Early diagnosis, discontinuation of the culprit drug, and timely treatment are imperative in the management of the condition. Due to a potential genetic predisposition to DRESS, clinicians should use caution when treating first-degree family members with the same class of medication that was problematic for their relative. Long-term sequelae, such as Grave's disease and diabetes mellitus, have been reported following DRESS. Therefore, long-term monitoring with appropriate testing is recommended. JFP

References

1. Cacoub P, Musette P, Descamps V, et al. The DRESS syndrome: a literature review. *Am J Med*. 2011;124:588-597.
2. Husain Z, Reddy BY, Schwartz RA. DRESS syndrome: Part I. Clinical perspectives. *J Am Acad Dermatol*. 2013;68:693.e1-e14.
3. Bourgeois GP, Cafardi JA, Groysman V, et al. Fulminant myocarditis as a late sequelae of DRESS-2 cases. *J Am Acad Dermatol*. 2011;65:889-890.
4. Cho YT, Yang CW, Chu CY. Drug reaction with eosinophilia and systemic symptoms (DRESS): an interplay among drugs, viruses, and immune system. *Int J Mol Sci*. 2017;18:1-21.
5. Alfirevic A, Pirmohamed M. Drug-induced hypersensitivity and the HLA complex. *Pharmaceuticals* (*Basel*). 2011;4:69-90.
6. American College of Rheumatology. 1997 Update of the 1982 American College of Rheumatology Revised Criteria for Classification of Systemic Lupus Erythematosus. Available at: https://www.rheumatology.org/Portals/0/Files/1982%20SLE%20Classification_Excerpt.pdf. Accessed August 30, 2017.
7. Descamps V, Ben Saïd B, Sassolas B, et al. Management of drug reaction with eosinophilia and systemic symptoms (DRESS). *Ann Dermatol Venereol*. 2010;137:703-708.
8. Peyrière H, Dereure O, Breton H, et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? *Br J Dermatol*. 2006;155:422-428.
9. Pichler WJ, Tilch J. The lymphocyte transformation test in the diagnosis of drug hypersensitivity. *Allergy*. 2004;59:809-820.
10. Husain Z, Reddy BY, Schwartz RA. DRESS syndrome part II: management and therapeutics. *J Am Acad Dermatol*. 2013;68:709.e1-e9.
11. Funck-Brentano E, Duong TA, Bouvresses S, et al. Therapeutic management of DRESS: a retrospective study of 38 cases. *J Am Acad Dermatol*. 2015;72:246-252.