Case Report

Death Due to Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome: A Case Report

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Abstract

Background
Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a life-threatening, multi-organ adverse drug reaction with an incidence of 1 in 1000 to 1 in 10 000 high-risk drug exposures.

Case Presentation
An elderly female presented to the hospital with progressive weakness and a diffuse erythematous macular rash covering most of her body that started 3 days prior. Over the next 3 days, the patient quickly deteriorated, developing disorientation with acute onset left-sided weakness, leukocytosis, thrombocytopenia, eosinophilia, liver and kidney failure, and hypoxia. Clinical and histological changes supported the diagnosis of DRESS syndrome caused by intravenous (IV) ampicillin administered during a prior hospitalization for a urinary tract infection. Systemic corticosteroids were initiated quickly thereafter, but the patient ultimately succumbed to complications caused by DRESS syndrome.

Conclusion
There are currently no randomized trials evaluating treatments for DRESS, and evidenced-based guidelines are lacking. Viral reactivation has also been suggested as a possible complication of DRESS syndrome, though the true incidence and association remain unclear. Although we started our patient on high-dose IV corticosteroids early in her course, she still succumbed to complications of DRESS syndrome. Further research into the treatment of DRESS syndrome and its association with viral reactivation is essential.

Keywords
DRESS syndrome; drug reaction; ampicillin; drug hypersensitivity syndrome; intravenous ampicillin; severe cutaneous adverse reaction

Introduction
Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a life-threatening, multi-organ adverse drug reaction with an incidence of 1 in 1000 to 1 in 10 000 high-risk drug exposures. Symptoms typically occur 2-6 weeks after drug exposure and can last months. Aromatic anticonvulsants and allopurinol most commonly cause DRESS, but antibiotics and antivirals have been implicated as well.[1,2] DRESS syndrome is generally characterized by an exanthematous morbilliform rash accompanied by fever, lymphadenopathy, hematologic findings, and multi-organ involvement.[2] The pathogenesis of DRESS is controversial but has been associated with specific medications, human leukocyte antigen alleles, an altered immune response, and, most recently, the reactivation of the human herpes virus.[2,3] Here we describe a case of DRESS syndrome caused by ampicillin. The patient was quickly treated with intravenous corticosteroids, the current leading recommendation, but corticosteroid treatment remains controversial.

Case Presentation

An elderly female with a past medical history of atrial fibrillation and dementia presented to the emergency department (ED) due to progressive weakness over the past few weeks. The patient also exhibited a diffuse erythematous macular rash covering the majority of her body that started 3 days earlier. The patient was admitted to the hospital 12 days before her first visit to the ED for atrial fibrillation with a rapid ventricular response and an asymptomatic urinary tract infection (UTI). At that time, she was started on a diltiazem drip for atrial fibrillation, intravenous (IV) ampicillin for the UTI, and eventually transitioned to oral diltiazem, apixaban, and levofloxacin. After discharge, the rash started 1 day after taking her first dose of oral levofloxacin. The rash never improved despite a visit to her primary care physician and the discontinuation of all medications. During her second presentation to the hospital, the rash was slightly itchy, but the patient did not complain of other systemic symptoms. Her labs were significant for an elevated white blood cell (WBC) count at 18.44 x 10^9/L and a urinalysis that showed 1+ bacteria, 6-10 x 10^9/L WBC, trace leukocyte esterase, and the presence of eosinophils. Dermatology was consulted, and her physical exam was only significant for a diffuse erythematous macular rash (**Figure 1**) with no mucosal lesions. Her vitals were all within normal limits, and she was alert and oriented to person, place, and time. She was diagnosed with an exanthematous drug eruption due to the levofloxacin and started on topical triamcinolone 0.1% 2 times a day (BID) with oral antihistamines for itching. A punch biopsy was taken and sent to pathology.

Over the next 3 days, the patient started to deteriorate. She was no longer alert or oriented and developed acute onset left-sided weakness. A head computed tomography (CT) scan, head/neck CT angiography, and brain magnetic resonance imaging were all performed and were found to be unremarkable. WBC increased to 23.12 x 10^9/L; platelets decreased from 238 x 10^9/L to 67 x 10^9/L; and eosinophils increased from 2.4% x 10^9/L to 7.8% x 10^9/L. Atypical lymphocytes were found on a peripheral smear. Kidney and liver function also started declining with blood urea nitrogen/creatinine ranging from 32 ± 1.04 mg/dL to 46 ± 1.22 mg/dL. Aspartate aminotransferase increased from 67 units/L to 103 units/L, and alkaline phosphatase remained elevated at 131 U/L. A CT of the abdomen and pelvis was also performed, which showed persistent renal cortical enhancement, suggesting acute renal failure. The patient began going in and out of atrial fibrillation and was acutely short of breath. An arterial blood gas showed a CO_2 of 25.2 mmHg, HCO_3 of 15.1 nmol/L, pO2 of 70.9 mmHg, and an O_2 saturation of 94.3%. She was started on a 2L O_2 nasal cannula. Upon physical exam, the rash had become acutely coalescent and covered an increased body surface area (**Figure 2**). The patient developed acute facial edema along with cervical and supraclavicular lymphadenopathy. The punch biopsy results showed a relatively unremarkable stratum corneum overlying an epidermis that showed mild acanthosis and mild spongiosis. Exocytosis of rare eosinophils (**Figure 3A**) and rare, small, cytologically bland, mature-appearing lymphocytes present. The dermis contained a superficial, perivascular and interstitial, chronic inflammatory cell infiltrate composed of mostly bland lymphocytes (**Figure 3B**). The histological changes in the presented clinical context supported the ultimate diagnosis of DRESS syndrome, likely due to the IV ampicillin administered 2 weeks prior.

Given that levofloxacin was administered to the patient 24 hours prior to rash onset, the

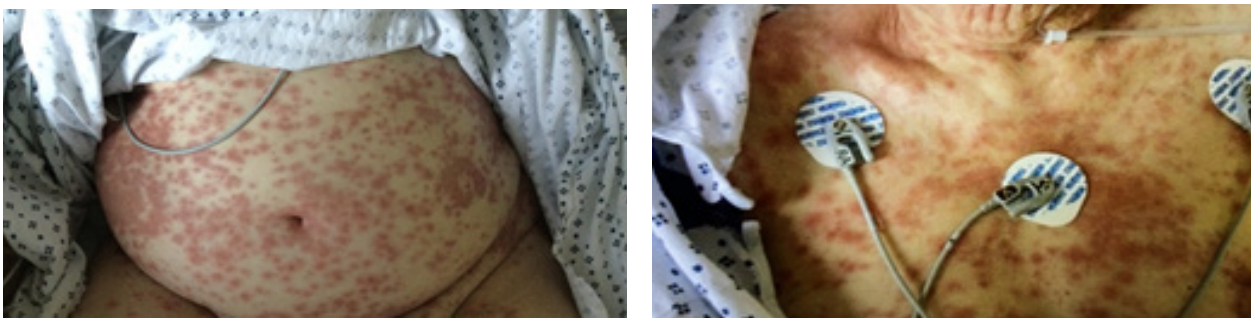

Figure 1. An erythematous macular rash was present on the initial exam during hospital admission.

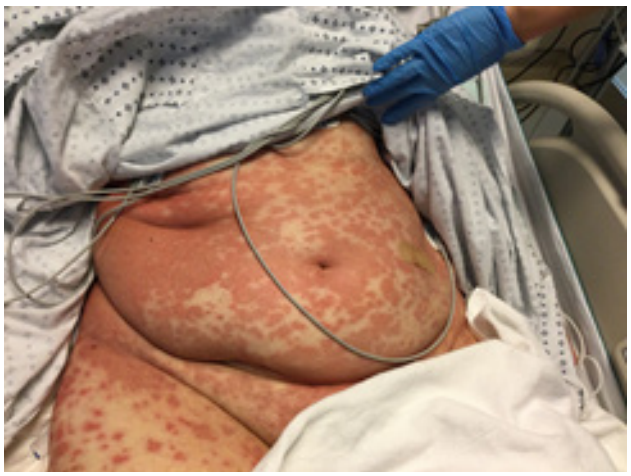

Figure 2. On day 3 of hospital admission, the rash had become acutely coalescing and covered an increased body surface area.

drug was ruled out as the causative medication. All antibiotics were immediately discontinued on day 3 of hospitalization, and the patient was started on IV methylprednisolone 60 mg BID. It was recommended that the patient be slowly tapered down from steroids over 6-8 weeks. Antinuclear antibodies test, blood cultures, and a thyroid-stimulating hormone test were all negative. The medical team was instructed to closely monitor the patient for continued renal, hepatic, cardiac, neurologic, pulmonary, and thyroid involvement. Ultimately, the patient continued to decline and was transferred to comfort care with the withdrawal of all life-sustaining medications. She became apneic and pulseless, and she passed away 5 days after steroid initiation due to the complications of DRESS syndrome.

Discussion

DRESS is an immune-mediated, systemic, drug-induced reaction. It is an under-recognized and potentially fatal syndrome that is often challenging to diagnose based on its various presentations. However, with a reported mortality rate of around 10%, the consequences of misdiagnosis can be fatal. The prevalence ranges from 1 in 1000 to 1 in 10 000 high-risk drug exposures and frequently occurs in females. Symptoms typically occur 2-6 weeks after drug exposure and can last months after medication discontinuation. Aromatic anticonvulsants and allopurinol most commonly induce DRESS. However, many reports have indicated that antibiotics and antivirals are causes as well.[1,2] The pathogenesis of DRESS has been associated with specific medications, human leukocyte antigen alleles, an altered immune

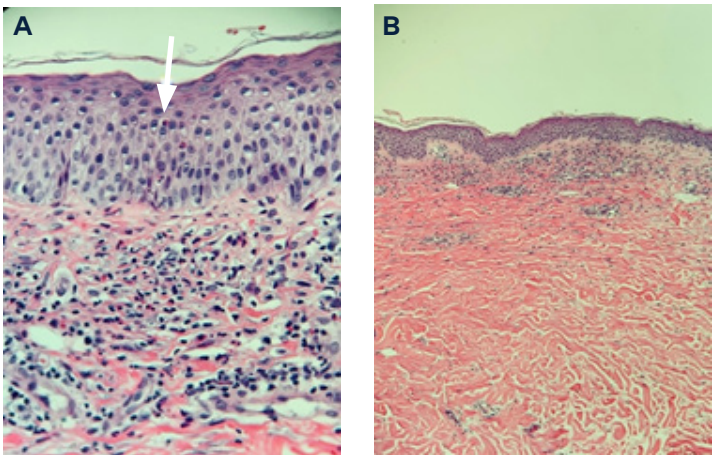

Figure 3. Histopathology revealed signs of DRESS syndrome. A) A punch biopsy revealed mild acanthosis and spongiosis along with exocytosis of rare eosinophils (white arrow). B) A low-power view shows findings confined to the epidermis and papillary dermis.

response, and, most recently, the reactivation of the human herpes virus. It has been suggested that DRESS activates Th2 lymphocytes and CD8 cells that affect the skin and internal organs.[2,3]

DRESS syndrome is generally characterized by an exanthematous morbilliform rash accompanied by fever, lymphadenopathy, and hematologic findings, including leukocytosis with hypereosinophilia and multi-organ involvement. Systemic involvement typically occurs 1-2 weeks after the initial rash. The most commonly affected organs are the liver, kidney, lungs, and heart. Involvement of the central nervous system (CNS), thyroid, pancreas, colon, muscles, and serosa have also been reported. Fulminant hepatitis is the most common cause of death (5-10% of cases).[2,4] Overall, symptoms are quite variable. Because of this, specific criteria have been developed to aid in diagnosis. The European Registry on Severe Cutaneous Adverse Drug Reactions (RegiSCAR) is the most commonly used tool. Greater than 5 points gives a definite diagnosis of DRESS with criteria including fever, lymphadenopathy in greater than 2 sites, atypical lymphocytes, peripheral hypereosinophilia, characteristic skin involvement, internal organ involvement, rash lasting longer than 15 days, and blood work ruling out other causes.[1,2] Although a skin biopsy helped make the final diagnosis of DRESS in our patient, it is essential to note that a biopsy is not mandatory to make the diagnosis.[5]

The severity of antibiotic-induced DRESS syndrome when comparing antiepileptics and allopurinol is controversial. However, a recent report argued that antibiotic-induced DRESS syndrome that required hospital admission was associated with shorter drug latency, an extended hospital stay, and increased mortality.[6] In a review by Sharefzadeh et al, only about 8.6% of over 250 cases of DRESS syndrome were caused by penicillins, and of the reported cases, none were fatal.[2] As far as we know, there have been no reported cases of ampicillin-induced DRESS syndrome resulting in a fatal outcome. The findings from our case are significant for physicians who work in a hospital setting where IV antibiotics are given frequently. Our case highlights the importance of evaluating antibiotic necessity before they are given and keeping all beta-lactams in mind when trying to deduce the cause of a cutaneous drug reaction. Most importantly, DRESS needs to be considered in the differential.

Although not as common, neurologic symptoms associated with DRESS syndrome have also been reported. There is a proposed link between the degree of hypereosinophilia and CNS findings in this patient population.[4] While there have been several reports of encephalopathy in DRESS syndrome, what is unique about our patient was her altered mental status and focal neurologic deficits without any pathology on brain imaging. There is only one other report of DRESS syndrome with similar CNS findings.[7] This fact highlights the importance of recognizing less common manifestations of DRESS syndrome, particularly neurologic symptoms. Also, in forming the differential of stroke-like symptoms in a hospitalized patient, we urge physicians to consider DRESS syndrome, especially in patients presenting with concomitant cutaneous symptoms.

It is imperative that physicians diagnose and treat DRESS syndrome as quickly as possible to prevent unfortunate outcomes such as death. In a summary of fatal DRESS syndrome cases by Cacoub et al, the average age of death was 49, and the average time between symptoms and death was 6.2 weeks.[1] At age 90+, our patient was significantly older and rapidly decompensated in less than 2 weeks. Once the diagnosis is made, it is critical to remove the offending drug. Although there have been no randomized controlled trials evaluating the use of glucocorticoids, systemic corticosteroids are recommended when there is internal organ involvement along with symptomatic treatment and support.[4] If systemic steroids are insufficient, IV immunoglobulin can be administered adjunctively.[3] There are no current guidelines for the optimal length of treatment. However, there have been many cases of rebound when steroids are tapered off too early. Therefore, it is essential to taper corticosteroids over no less than 6-8 weeks.[4,7] Recently, a retrospective case-control study showed shorter cessation of progression, quicker resolution of erythema, shorter duration of hospital stay, and faster normalization of fevers, leukocytosis, eosinophilia, and liver function tests with the use of cyclosporine over corticosteroids.[8] Other researchers have evaluated Janus kinase inhib-

itors, plasmapheresis, rituximab, and valganciclovir as treatment considerations, but routine use has not been recommended.[9]

DRESS syndrome is characteristically associated with sequential reactivation of herpesviruses (human herpesvirus 6 [HHV-6], Epstein-Barr virus [EBV], and cytomegalovirus [CMV]). Since systemic corticosteroids are believed to result in viral reactivation due to their immunosuppressive effects, it seems crucial that the next steps in research would include clarifying the influence of systemic steroids on viral reactivation in this potentially deadly drug reaction. A 2020 study following 20 patients with DRESS syndrome in a Japanese hospital between 2002 and 2016 attempted to characterize some of these effects.[10] They found that high-dose corticosteroids started within 1 week after onset tended to inhibit the occurrence of HHV-6 reactivation, while low-dose corticosteroids or late-start high-dose corticosteroids did not suppress the occurrence of viremia. Increased CMV viral load, on the other hand, was found to be increased by corticosteroids, regardless of the start time. CMV-positive cases traditionally have been associated with older age and complications associated with a fatal course.[10] This result may indicate the necessity to test future patients with DRESS syndrome for viral DNA before initiating high-dose corticosteroids, especially relevant to our patient in this case. Further research in this area may be needed to further characterize the role viral reactivation plays in DRESS syndrome, which may reduce DRESS-related death.

Conclusion

In this report, we present a rare case of death due to DRESS syndrome in an elderly female and discuss its current diagnostic criteria and treatment recommendations. This case not only resulted in death but also presented with acute stroke-like symptoms, likely caused by IV ampicillin, making it a unique case to examine. There are currently no randomized trials evaluating treatments for DRESS, and evidenced-based guidelines are lacking. Although we administered high-dose IV corticosteroids early in her course, the patient ultimately succumbed to complications of DRESS syndrome. Further research is essential for treating DRESS syndrome due to its association with viral reactivation and the implications that currently recommended corticosteroids can have on a patient's clinical course.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Dr Sternad is an employee of LewisGale Hospital Montgomery, a hospital affiliated with the journal's publisher.

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