

CASE REPORT

The DRESS Syndrome: The Great Clinical Mimicker

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The life-threatening DRESS (drug rash with eosinophilia and systemic symptoms) syndrome is characterized by the presence of at least three of the following findings: fever, exanthema, eosinophilia, atypical circulating lymphocytes, lymphadenopathy, and hepatitis. This syndrome is difficult to diagnose, as many of its clinical features mimic those found with other serious systemic disorders. This idiosyncratic reaction occurs most commonly after exposure to drugs such as allopurinol, sulfonamides, and aromatic anticonvulsants such as phenytoin, phenobarbital, and carbamazepine. We describe a 44-year-old woman who was brought to the emergency department with new-onset hemorrhagic stroke. She was admitted to the intensive care unit where she received supportive care that included clonidine and hydralazine for blood pressure control and phenytoin for seizure prophylaxis. On hospital day 21, the patient developed signs and symptoms of severe sepsis. Despite receipt of broad-spectrum antibiotics (vancomycin and piperacillin-tazobactam) and supportive care, the patient's clinical condition worsened with progressive jaundice, severe oliguria, and labile blood pressures. All cultures revealed no growth, and her chest radiograph remained clear. Several days after the onset of her fever, the patient developed several hematologic abnormalities including thrombocytopenia, with schistocytes present on a peripheral smear. She also had an elevated lactate dehydrogenase level. A provisional diagnosis of thrombotic thrombocytopenic purpura was made; however, the patient then developed severe facial edema, nearly global erythroderma, and severe exfoliative dermatitis. A punch biopsy of the skin was compatible with the DRESS syndrome. Phenytoin, vancomycin, and piperacillin-tazobactam were discontinued, and the patient was started on systemic corticosteroids, with rapid resolution of her fever and eosinophilia and progressive improvement in her skin rash and multiorgan system dysfunction. Use of the Naranjo adverse drug reaction probability scale indicated a probable relationship (score of 5) between the patient's development of DRESS syndrome and treatment with phenytoin. Clinicians should have a high index of suspicion for the DRESS syndrome in patients being treated with aromatic anticonvulsants who develop a sepsis-like syndrome. Furthermore, considering the potential severe effects associated with phenytoin, the risks and benefits should be carefully evaluated before using this agent for seizure prophylaxis.

Key Words: DRESS syndrome, eosinophilia, drug reaction, phenytoin, TTP, thrombotic thrombocytopenic purpura, thrombocytopenia, sepsis, hypersensitivity reaction, exanthema.

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allopurinol, sulfonamides, and aromatic anti-convulsants such as phenytoin, phenobarbital, and carbamazepine.¹⁻³ The syndrome is defined by the presence of at least three of the following findings: fever, exanthema, eosinophilia, atypical circulating lymphocytes, lymphadenopathy, and hepatitis.¹⁻⁵ We describe a patient with the DRESS syndrome, probably caused by phenytoin, whose clinical presentation closely mimicked that of sepsis and thrombotic thrombocytopenic purpura (TTP).

Case Report

A 44-year-old, morbidly obese (body mass index of 43.8 kg/m²), African-American female was brought to our emergency department with headache, nausea, vomiting, and loss of consciousness. Neurologic examination revealed a left hemiparesis with a fluctuating level of consciousness. A computerized tomographic scan of the brain demonstrated a right-sided hemorrhagic stroke. The patient's medical history was significant for hypertension, type 2 diabetes mellitus, and a previous ischemic stroke.

The patient was endotracheally intubated and admitted to our intensive care unit (ICU) where she received supportive care that included clonidine 0.3 mg every 8 hours and hydralazine 50 mg every 6 hours for blood pressure control and phenytoin 150 mg every 8 hours for seizure prophylaxis. Due to an inability to wean from the ventilator, a tracheotomy was performed, and the patient was transferred on hospital day 16 to our step-down unit. Clonidine, hydralazine, and phenytoin were continued at the same dosages, and amlodipine 10 mg/day, metoprolol 50 mg every 12 hours, famotidine 20 mg/day, simvastatin 40 mg/day, and insulin lispro (sliding scale) were started. Five days after transfer to the step-down unit (day 21), the patient became febrile, with a body temperature spiking at 39.5°C, and hypotensive with worsening renal function and leukocytosis. A nosocomial infection with severe sepsis was suspected. Blood, urine, and endobronchial cultures and a chest radiograph were performed.

The patient was readmitted to the ICU and administered empiric antibiotic treatment with intravenous vancomycin 1000 mg every 12 hours

and piperacillin-tazobactam 3.375 g every 6 hours. She was resuscitated with intravenous fluids and a norepinephrine infusion titrated to achieve a mean arterial pressure above 65 mm Hg. Despite these interventional therapies, the patient's clinical course worsened with progressive jaundice, severe oliguria, and labile blood pressures. Blood and urine culture results were negative, a few colonies of *Pseudomonas aeruginosa* were isolated from the endobronchial culture, and chest radiograph findings were clear.

Several days after the onset of her fever, the patient developed several hematologic abnormalities including leukocytosis, eosinophilia, normocytic anemia, and thrombocytopenia with schistocytes present on a peripheral blood smear (Figure 1). She had an elevated lactate dehydrogenase (LDH) level as well as increasing bilirubin, blood urea nitrogen, and serum creatinine concentrations, and an increasing international normalized ratio. A provisional diagnosis of TTP was entertained, and preparation was made for plasmapheresis. However, the next day the patient was noted to have severe facial edema, nearly global erythroderma, and a severe exfoliative dermatitis that spared the mucosa (Figure 2).

Due to the concern of a potential drug hypersensitivity syndrome, phenytoin (after 24 days of treatment), vancomycin, and piperacillin-tazobactam were discontinued. The patient had no reported drug allergies and had not been previously treated with an aromatic anticonvulsant. A punch biopsy of the skin was compatible with the DRESS syndrome (Figure 3). Human herpesvirus 6 immunoglobulin M and polymerase chain reaction results were negative. The patient was

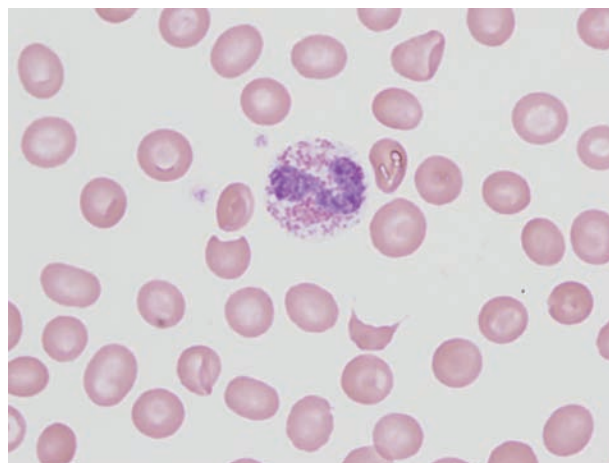


Figure 1. Peripheral blood smear on high-power field showing a single schistocyte.

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administered systemic corticosteroids with methylprednisolone 60 mg intravenously every 6 hours, with rapid resolution of her fever and eosinophilia. Over the next several days, there was progressive improvement in her skin rash and multiorgan system dysfunction. The patient was subsequently transferred back to the step-down unit for further rehabilitation. The evolution of her pertinent laboratory results are presented in Table 1.

Discussion

Our patient's case illustrates the difficulty in diagnosing the DRESS syndrome, which, due to its multitude of clinical features, mimics a number of serious systemic disorders. Our patient's initial presentation of fever, hypotension, and progressive organ failure in the hospital setting evoked the diagnosis of sepsis. However, no source of sepsis was identified, and all bacterial cultures were negative.

After several days of antibiotic therapy, the patient's clinical and hematologic findings appeared consistent with TTP. The patient had four of the "pentad of clinical findings" typical of TTP: fever, anemia, thrombocytopenia, and renal failure.⁶ As our patient was obtunded after her admission for hemorrhagic stroke, changes in her mental status (the fifth finding of the pentad) were difficult to detect. The presence of schistocytes on a peripheral blood smear appeared to confirm the diagnosis. However, on closer examination, a number of factors suggested that

Table 1. Laboratory Results During the Patient's Hospitalization

Laboratory Test	Day 21	Day 24 ^a	Day 28
Hemoglobin (g/dl)	8.6	7.4	7.3
Platelet count ($\times 10^3/\text{mm}^3$)	258	217	73
Eosinophils (%)	< 5	25	0
White blood cell count ($\times 10^3/\text{mm}^3$)	16.7	21.2	10.8
Lactate dehydrogenase (U/L)	ND	1419	576
Serum creatinine (mg/dl)	2.1	5.4	5.0
Troponin T (ng/ml)	ND	0.21	0.06
AST (U/L)	84	527	210
ALT (U/L)	38	157	127
Total bilirubin (mg/dl)	0.2	2.9	12.8
Albumin (g/dl)	3.0	1.9	2.6

ND = not done; AST = aspartate aminotransferase; ALT = alanine aminotransferase.

^aPhenytoin was started on day 1 and stopped on day 24.

this diagnosis was less likely. It is uncommon for TTP to develop as a complication in a hospitalized patient. Although our patient was mildly anemic, TTP usually presents with a severe anemia, as red blood cells are cleaved by the fibrin-platelet meshwork.⁷ The average platelet count in patients with TTP is approximately $25 \times 10^3/\text{mm}^3$; our patient's lowest count was $64 \times 10^3/\text{mm}^3$. Typically patients with TTP have two or more schistocytes on each high-power field⁶; our patient had only isolated schistocytes identified on a peripheral smear (Figure 1). Furthermore, the LDH level typically rises as the platelet count falls, but our patient's LDH level peaked early during her ICU stay although her platelet count continued to fall. In addition, high fever is an unusual presenting feature of TTP.⁷ Finally, when the global erythroderma and

A



B



Figure 2. The patient's severe facial edema (A) and nearly global erythroderma and severe exfoliative dermatitis (B).

morbilloform exanthema became apparent, the diagnosis of a drug hypersensitivity reaction became more likely. It is possible that the DRESS syndrome was not recognized earlier in our patient because of her natural dark skin color.

Use of the Naranjo adverse drug reaction probability scale⁸ indicated a probable relationship (score of 5) between the patient's development of the DRESS syndrome and treatment with phenytoin. Severe thrombocytopenia with evidence of hemolysis (mimicking TTP) has occurred in patients with the DRESS syndrome, but the presence of schistocytes has not been reported previously.⁷

The first documented cases of the DRESS syndrome can be traced to hydantoin drugs as early as the 1930s, although a formal name for the syndrome was not coined until the 1980s. The syndrome then became known by several names: the drug hypersensitivity syndrome, anticonvulsant hypersensitivity syndrome, and phenytoin hypersensitivity syndrome.^{4, 9–11} The name “drug rash with eosinophilia and systemic symptoms” was first introduced in 1996 to decrease the equivocality of the term “hypersensitivity syndrome.”¹²

The DRESS syndrome is most frequently caused by aromatic anticonvulsants (phenytoin, phenobarbital, and carbamazepine); however, other drugs such as sulfonamides, metronidazole, minocycline, sulfasalazine, allopurinol, and antiretrovirals such as nevirapine and abacavir

have been implicated.^{2, 4} The incidence of the DRESS syndrome due to aromatic anticonvulsants is approximately 1/5000 exposures. African-American race and a family history of DRESS syndrome are associated with an increased risk of the syndrome. The onset of the disease has been reported to be 2–86 days (mean 35 days) after starting the offending drug.⁴ Rechallenge will result in recurrence of the syndrome with cross-reactivity occurring between the aromatic anticonvulsants.^{1, 10} A high fever (up to 41°C) is a common presenting finding.^{2, 4} The skin rash is usually maculopapular and/or erythrodermic; however, bullous and erythematopustular rashes have been reported. Facial edema is common.

The pathogenesis of DRESS is complex and not fully understood. It has been proposed that DRESS occurs due to abnormal breakdown of drug metabolites that in turn cause abnormalities in T-cell function. In the case of anticonvulsants, the proposed mechanism is an inherited deficiency of the enzyme epoxide hydroxylase, which converts arene oxide to *trans*-dihydrodiols. Sulfonamides cause DRESS in patients who are slow acetylators, producing toxic hydroxylamine metabolites. Recently human herpesvirus 6 has been implicated in the development of DRESS.^{5, 13}

The most important steps in managing patients with DRESS are recognizing the presence of this syndrome and immediately stopping the offending drug. Management is essentially supportive. The role of corticosteroids and intravenous immunoglobulins in the treatment of DRESS syndrome are controversial.^{10, 11} Our patient appeared to show dramatic improvement after starting a corticosteroid; however, it is unclear whether the resolution of the DRESS syndrome was related to the initiation of this drug. It should be noted that the most recent stroke guidelines from the American Heart Association–American Stroke Association (AHA-ASA) make no specific recommendations regarding seizure prophylaxis in patients with ischemic stroke.¹⁴ However, in patients with intracerebral and subarachnoid hemorrhage, the routine use of phenytoin has been associated with cognitive impairment and worse neurologic outcomes; thus, the AHA-ASA no longer recommends the routine long-term use of anticonvulsants in this setting.^{15–19}

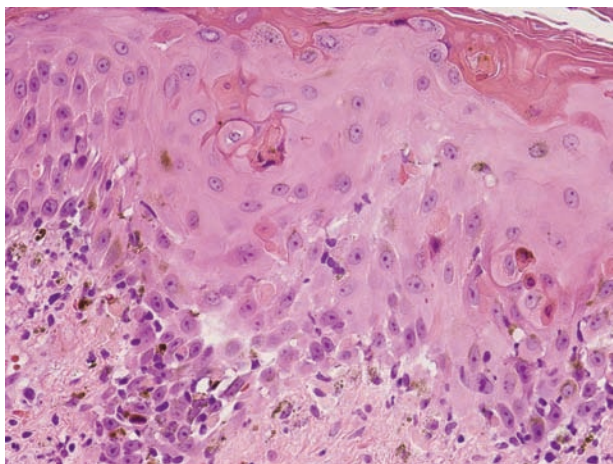


Figure 3. Hematoxylin and eosin stain of the skin biopsy specimen on high-power field showing interface dermatitis, superficial perivascular inflammation, papillary dermal edema, and hemorrhage. The pathologic differential diagnosis was recorded as hypersensitivity drug syndrome versus viral exanthema.

Conclusion

Our case report highlights the difficulty in diagnosing the DRESS syndrome. Clinicians

should have a high index of suspicion for the DRESS syndrome in patients being treated with aromatic anticonvulsants who develop a sepsis-like syndrome. Furthermore, considering the potential severe adverse reactions associated with phenytoin, the risks and benefits should be carefully evaluated before using this agent for seizure prophylaxis.

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