Severe DRESS Syndrome Managed With Therapeutic Plasma Exchange

abstract

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a rare but increasingly described phenomenon of immune activation and organ dysfunction in association with a wide variety of medications. This reaction shows a broad spectrum of clinical presentation and severity, ranging from mild to lethal. Treatment strategies of immune suppression appear helpful in some cases, but treatment failures occur frequently with reported mortality rates of 5% to 10%. We present a pediatric case of DRESS syndrome associated with either lamotrigine or bupropion, leading to multiorgan involvement and life-threatening complications of respiratory failure and cardiac arrest. After failing to improve with removal of these medications and administration of systemic corticosteroids, our patient showed dramatic, sustained clinical response to therapeutic plasma exchange. To our knowledge, this is the first reported case of therapeutic plasma exchange used for life-threatening DRESS syndrome in a pediatric patient. This case suggests needed research for this therapeutic option in life-threatening DRESS syndrome resistant to high-dose steroids. Pediatrics 2013;131:e945–e949
DRESS syndrome is a type of drug hypersensitivity defined by a constellation of findings associated with hyperinflammation related to a medication exposure. The syndrome or a variation has been described in the literature since the 1950s under the names drug-induced pseudolymphoma, anticonvulsant hypersensitivity syndrome, drug-induced delayed multiorgan hypersensitivity syndrome, and drug-induced hypersensitivity syndrome.1–5 Kardaun et al describe the following general features of hypersensitivity syndrome/DRESS syndrome: drug-induced immunologic background, later onset than other drug reactions, longer duration than common “drug rashes,” multiorgan involvement, lymphocyte activation, eosinophilia, and frequent virus reactivation.

Although it was initially reported in association with anticonvulsant medications,2 it has since been associated with most medication classes.6 Bocquet et al first presented the name DRESS during a review of what was previously termed hypersensitivity syndrome.3 As initially defined by Bocquet et al, DRESS diagnostic criteria required cutaneous drug eruption, hematologic abnormalities, and systemic involvement.3 The nomenclature DRESS may cause confusion because eosinophilia is not required to make the diagnosis. The diagnosis is particularly challenging because of delayed symptom onset, the wide spectrum of clinical presentation and organ involvement, and the variety of nomenclature for the syndrome.7,8

**CASE DESCRIPTION**

A 14-year-old African American girl with no significant medical history was admitted to an inpatient psychiatric unit for suicidal ideation, diagnosed with bipolar disorder, and treated with lamotrigine and bupropion.

Seventeen days after initiation of these 2 medications, she developed a generalized erythematous skin rash, high-grade fevers, and lymphadenopathy. She presented to an emergency department, where she was prescribed clindamycin for acute lymphadenitis. Two weeks later, she was admitted to the hospital with fever, rash, diffuse tender lymphadenopathy, painful exudative pharyngitis, and glossitis. Laboratory investigation revealed transaminitis, eosinophilia, and atypical lymphocytes, leading to concern for an adverse drug reaction. Lamotrigine and bupropion were stopped, and the patient improved with supportive care. She was discharged, only to return twice with generalized pain, fever; severe painful exudative pharyngitis, and glossitis. Workup was negative for antinuclear antibody; double-stranded DNA; HIV; Epstein-Barr virus (EBV); cytomegalovirus (CMV); hepatitis A, B, and C; streptococcal pharyngitis; urinary tract infection; bacteremia; human herpes virus type 6 titer; and mononucleosis.

She was transferred to a tertiary care center for management of acute kidney injury 46 days after the initiation of lamotrigine and bupropion. Around the time of transfer, she had improvement in her skin rash and hepatitis but suffered from volume overload, anemia, pancreatitis, kidney injury, and thyroiditis. A percutaneous ultrasound-assisted renal biopsy revealed severe acute and subacute tubulointerstitial nephritis with granulomatous inflammation. Systemic steroids (intravenous methylprednisolone 250 mg daily) were started on day 49, and her renal function began to improve. However, on day 50, she developed respiratory distress, necessitating intensive care. Two days later, on day 52, she was intubated for hypoxic respiratory failure. Much later in the same day, she had a 6-minute cardiac arrest secondary to torsades de pointes. She received 1 dose of epinephrine and 1 episode of cardioversion with subsequent return of spontaneous circulation. At the time of cardiac arrest, magnesium level was 1.9 mg/dL, and potassium level was 5.0 mmol/L. Her QTc was prolonged to 521 ms hours before the cardiac arrest. Her QT interval was normal on admission to the tertiary care center and normal on follow-up as an outpatient. The etiology of her QT prolongation, torsades de pointes electrical rhythm, and cardiac arrest is not clear but could have been secondary to systemic inflammation or myocarditis or possibly medication effect. She did not receive any known QT prolonging medication on the day of the arrest.

In light of her rapidly progressive clinical deterioration in the setting of DRESS syndrome and incomplete response to IV corticosteroids, we elected to proceed promptly with plasma exchange (PLEX), although we also considered intravenous immunoglobulin (IVIg), immunomodulators, and the continuation of high-dose steroids. PLEX was performed every other day for a total of 4 procedures. One plasma volume was exchanged with each procedure, and 5% albumin was used as replacement. She tolerated all the procedures well. Within 12 hours of the first PLEX session, her course improved dramatically. She finally became afebrile, her pancreatic enzymes decreased by 50% from 6059 to 3051 U/L. C-reactive protein fell rapidly, and she was extubated without complication 4 days after initiation of PLEX. Her endomyocardial biopsy performed 4 days after initiation of PLEX did not show signs of inflammation or eosinophilia. Her liver function, renal function, and eosinophilia continued to trend positively and she was discharged on day 68 with a slow prednisone taper over 2 months in attempt to continue to suppress inflammation. In follow-up 3 weeks after discharge, she showed continued clinical and laboratory improvement. At 3 months, she was asymptomatic, with normal laboratory values except for treated hypothyroidism (Figure 1).
DISCUSSION

Using the RegiSCAR scoring system proposed by Kardaun et al, our patient had a “definite” case of DRESS. Additionally, our patient met the criteria for the diagnosis of DRESS or “atypical drug-induced hypersensitivity syndrome” under the criteria set forth by Bocquet et al and the Japanese consensus group, respectively. Despite meeting diagnostic criteria, our patient’s asynchronous timing of clinical manifestations made the diagnosis difficult. Her skin rash and hepatitis were improving when she first showed signs of acute kidney injury. The exact onset of thyroid and pancreatic involvement is unclear. Her pulmonary and cardiac symptoms did not present clinically until her rash had resolved and hepatitis was improving. The exact etiology of her cardiac arrest remains unclear because her endomyocardial biopsy and cardiac enzyme levels were normal. Notably, our patient had evidence of inflammation in 6 organ systems in addition to the hematologic and skin abnormalities.

The pathogenesis of DRESS remains incompletely understood. At least 44 drugs have been reported to be associated with DRESS, including, most frequently, aromatic anticonvulsants. Lamotrigine is a well-described medication leading to DRESS syndrome. Bupropion has not been shown to cause DRESS but has been associated with mild serum sickness reactions. Clindamycin has not been associated with DRESS and is temporally unlikely to be the culprit medication in our case. Suggested mechanisms for DRESS and other hypersensitivity syndromes include reactive metabolites leading to stimulation of CD4+ and CD8+ T cells through a variety of mechanisms, and interleukin-5 and tumor necrosis factor (TNF)-α release from CD4+ and CD8+ cells, resulting in activation of eosinophils and inflammation. In DRESS syndrome specifically, studies have shown an oligoclonal proliferation of activated virus-specific and nonspecific T cells resulting from sequential reactivation of the herpes viruses HHV-6, HHV-7, EBV, and CMV, especially in the setting of drug-induced hypogammaglobulinemia permitting viral reactivation. Parvovirus B19 and mycoplasma can lead to findings similar to DRESS syndrome. Our patient had negative EBV, CMV, and HHV-6 titers. We did not assess for HHV-7 reactivation, mycoplasma infection, or parvovirus B19 infection.

The management of DRESS calls for early recognition and withdrawal of offending medications. Current treatment is variable, and reports are conflicting. It is unclear if other drug reactions have similar enough

![FIGURE 1](Timeline of events (symptoms, laboratory markers of organ dysfunction, presentation to medical care, transfer to tertiary care center, and therapeutic interventions). **Exposure to lamotrigine and bupropion.)
pathogenesis that therapeutic trials of Stevens-Johnson syndrome or toxic epidermal necrolysis should directly inform treatment of DRESS. Systemic corticosteroids are the current cornerstone of treatment of DRESS. Options that have been successfully used in the face of clinical deterioration include pulsed methylprednisolone, other immunosuppressive agents such as cyclosporine and cyclophosphamide, and IVIg. Acute pancreatitis dampened enthusiasm for using pulse corticosteroids in this patient. Although adverse effects may accompany PLEX and IVIg administration, we favored these interventions because of their rapid onset of action. We chose PLEX over IVIg because a recent description of 6 patients with DRESS treated with IVIg suggested that risk outweighed benefits. Furthermore, we were concerned about volume overload with IVIg infusion. We were finally concerned that the cardiac arrest may have been due to myocarditis, and a recent reported case of DRESS with myocarditis responded to PLEX plus rituximab.

Increased circulating cytokines likely contribute to the pathogenesis of DRESS, and we reasoned that reduction of circulating cytokine levels would result in prompt clinical improvement. PLEX reduces systemic cytokines in other settings of acute systemic inflammatory disease. In a study of patients with life-threatening meningococcal infections, PLEX accelerated the decline in TNF-α as well as TNF soluble receptors. Similarly, PLEX has lowered circulating concentrations of TNF-α and interleukin-6 in patients with acute liver failure. Finally, a prospective trial comparing PLEX to standard of care for patients with sepsis and multiorgan system failure demonstrated a significant increase in survival of septic patients receiving PLEX. The reported action of PLEX to rapidly remove circulating cytokines in a nonspecific fashion and improve survival of septic patients was the basis for our decision to use PLEX in our patient. In summary, our patient showed unquestionable clinical deterioration despite lamotrigine and bupropion withdrawal for ≥2 weeks and 250 mg of methylprednisolone IV for 4 days. She was intubated, had a 6-minute cardiac arrest, and remained persistently febrile with continued signs of multiorgan dysfunction. We therefore proceeded with PLEX based on the above thought process and a previous report of using PLEX in the setting of DRESS and myocarditis. Our patient showed marked improvement of systemic inflammation and clinical condition coincident with our use of PLEX.

We feel that this outcome supports the hypothesis that PLEX can effectively and rapidly reduce morbidity and mortality in patients with inflammation like that encountered with DRESS that are resistant to corticosteroids. Furthermore, PLEX has fewer toxicities than are encountered with many other immunosuppressives. Given the paucity of evidence regarding treatment of acute systemic drug reactions, we advocate for a multicenter prospective randomized study of the efficacy of PLEX in DRESS and similar diseases.

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Pediatrics 2013;131;e945; originally published online February 18, 2013; DOI: 10.1542/peds.2012-2117
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*Pediatrics* 2013;131;e945; originally published online February 18, 2013;
DOI: 10.1542/peds.2012-2117

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