

Encephalopathy and strokes secondary to drug reaction with eosinophilia and systemic symptoms: A case report

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Clinical Implications

- A drug reaction with eosinophilia and systemic symptoms may arise from either vancomycin or ceftriaxone, and may be complicated by encephalopathy and strokes due to severe eosinophilia.
- Physicians treating drug reaction with eosinophilia and systemic symptoms should be aware of the possible rare complication of encephalopathy and strokes.

TO THE EDITOR:

A drug reaction with eosinophilia and systemic symptoms (DRESS) is a life-threatening hypersensitivity reaction that occurs within 2 months after drug exposure, commonly an antiepileptic drug, sulfonamide, minocycline, allopurinol, and abacavir.¹ DRESS is diagnosed by 3 of 4 criteria: fever, blood count abnormalities (hypereosinophilia and/or atypical lymphocytosis), systemic involvement (rash, hepatitis, carditis, and/or nephritis), and lymphadenopathy.¹ We report the case of a patient who developed DRESS from either vancomycin or ceftriaxone whose clinical course was complicated by encephalopathy and multiple strokes in the setting of severe eosinophilia. It is possible that early intervention of DRESS could prevent encephalopathy and stroke development, but larger studies are needed to support this.

A 67-year-old woman with severe eczema and bilateral hip replacements, with a chronically infected left hip that required debridement and an antibiotic spacer that contained vancomycin and tobramycin, and who was receiving intravenous vancomycin and ceftriaxone (for 4 weeks) presented with worsening left hip pain, rash, and a low-grade fever. On examination, her vital signs were temperature 36.9°C, blood pressure 121/95 mm Hg, heart rate 85 bpm, oxygen saturation 94%, and respiratory rate of 15 bpm. She had diffuse erythroderma of her arms, legs, trunk, torso, and face (Figure 1). Her left hip was mildly tender.

Her admission laboratory results showed a white blood cell count of 19,600/ μ L with 61% neutrophils and an absolute eosinophil count of 4300/ μ L (baseline count of 1200/ μ L 1 month earlier). Her admission creatinine level was 1.00 mg/dL. Her initial liver function tests were notable for an elevated alkaline phosphatase level of 442 U/L (from a previously normal baseline), with otherwise normal transaminases and bilirubin levels. A hip computed tomography (CT) showed a miniscule fluid collection near the left trochanter. Her vancomycin and ceftriaxone were stopped on hospital day 2 because of concern for drug allergy, and she was started on daptomycin instead. Wet wraps and triamcinolone cream were given for a possible eczema flare.

Over the next few days, her white blood cell count increased to 38,900/ μ L on day 6, with an evolving lymphocytosis (67% lymphocytes). A peripheral blood smear showed atypical lymphocytes. Her eosinophil count increased to 8700/ μ L on day 9. The origin of her leukocytosis was not clear because an infection workup was negative, including blood cultures, urinalysis, chest radiography, and a *Clostridium difficile* stool specimen. Her examination revealed new axillary, supraclavicular, and inguinal lymphadenopathy. She underwent a CT of the chest, abdomen, and pelvis, which showed extensive axillary, mediastinal, supraclavicular, retroperitoneal, iliac, and inguinal lymphadenopathy, and upper lung opacification. Her creatinine level increased to 1.70 mg/dL.

Her atypical lymphocytosis, eosinophilia, lymphadenopathy, rash, and elevated creatinine suggested a severe drug reaction. Additional testing was performed to exclude other causes of eosinophilia, and the patient was found to have negative stronglyloides antibody, cytoplasmic antineutrophil cytoplasmic antibodies of 1:40, perinuclear antineutrophil cytoplasmic antibodies of <1:40, negative HIV antibody and antigen, and negative antinuclear antibody. In addition, an EBV viral titer was negative. The opacification on her chest CT was thought to be eosinophilic pneumonitis consistent with a drug reaction. The allergy-immunology service was consulted, and intravenous methylprednisolone 60 mg twice daily was started on day 10 for likely DRESS. A skin biopsy showed interface and spongiotic dermatitis with eosinophils, which confirmed DRESS.

On day 10, the patient's mental status deteriorated. She was oriented only to person and was not speaking coherently. Her eosinophil count was elevated at 7900/ μ L. A head CT showed a small area of hypoattenuation and loss of gray-white matter differentiation in the posterior parieto-occipital portion of the left cerebral hemisphere, which was concerning for infarction. The neurology service was consulted, and thought that the patient was encephalopathic. A magnetic resonance imaging of the brain showed innumerable small areas of acute infarction in the cerebral and cerebellar hemispheres bilaterally (Figure 2). A magnetic resonance angiogram of the head and neck did not show flow-limiting stenosis, and a transesophageal echocardiogram did not reveal valvular vegetation or intracardiac shunt to explain her strokes. The patient's encephalopathy and infarctions were thought to most likely be secondary to her hypereosinophilia.

Her intravenous methylprednisolone was increased to 60 mg four times a day because she did not improve over 48 hours with 60 mg methylprednisolone twice daily. Gradually, her mental status, creatinine level, alkaline phosphatase level, white blood cell count, and eosinophil count improved, and, after 30 days, her intravenous methylprednisolone was tapered to oral prednisone. She was discharged to a rehabilitation facility. On discharge, a 21-day oral prednisone taper was planned. However, because the patient's rash flared with steroid tapering, 1 month later, her prednisone dose had to be increased again. Thereafter, she was again placed on a slow prednisone taper but experienced another flare 2 months later. She remains on a very slow prednisone taper now 11 months after the initial event.

This patient developed DRESS from either vancomycin or ceftriaxone, and her course was complicated by encephalopathy



FIGURE 1. Diffuse erythroderma noted on patient's admission physical examination.

and multiple strokes in the setting of hypereosinophilia. There is no diagnostic test with which we can implicate just one of these agents. Both antibiotics were started 2 months before admission, which makes either one likely as the causative agent. Although DRESS from these drugs is rare, it has been described.^{2,3}

However, neurologic manifestations with DRESS have not been extensively noted. O'Meara et al⁴ described a patient with DRESS with delirium in the absence of central nervous system pathology on brain imaging, but this type of presentation with encephalopathy is otherwise rare. Similarly, strokes have not been noted in the setting of DRESS secondary to vancomycin or ceftriaxone. Only 1 other case of stroke associated with DRESS was described, by Cahyanur et al,⁵ who reported a patient with DRESS who developed an ischemic parietal stroke after unknown antibiotic exposure. Although central nervous system complications with DRESS appear rare, they are noted in patients with hypereosinophilia. Both

generalized encephalopathy and strokes may rarely occur with hypereosinophilia.^{6,7} Encephalopathy is characterized by changes in behavior and by confusion, as observed in our patient, as well as upper motor neuron signs.⁷ Strokes occur in patients with hypereosinophilia at arterial border zone territories.⁶ Multiple mechanisms may contribute to the development of neurologic findings in hypereosinophilia. Cerebral strokes may occur from cardiac thromboembolism and microscopic angiopathy, direct eosinophil toxicity, or arterial thrombosis.⁶ Thrombosis may be related to eosinophilic hypothiocyannous acid production, which lead to a prothrombotic state.⁸ Encephalopathy may arise from small cerebral strokes or from direct eosinophil toxicity.^{6,7,9} We hypothesize that our patient's encephalopathy and strokes in the setting of DRESS were caused by hypereosinophilia because she improved with higher-dose corticosteroids and normalization of her eosinophil counts.

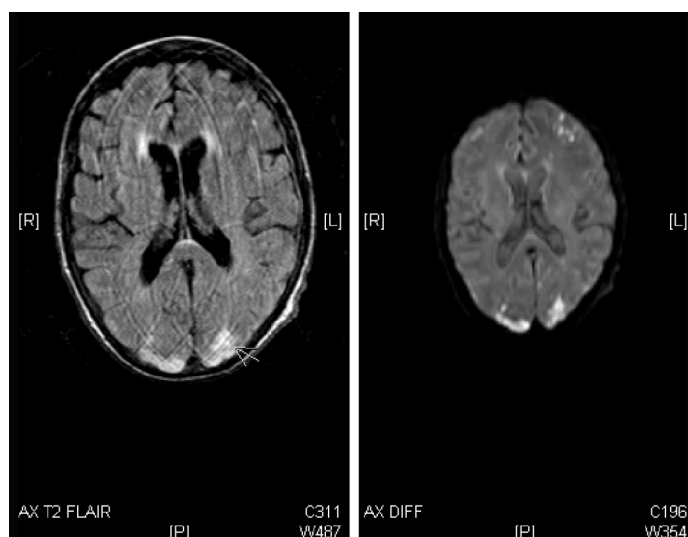


FIGURE 2. Magnetic resonance imaging of the brain (axial T2 flair and axial diffusion weighted), showing multiple strokes.

Treatment of DRESS includes discontinuation of the causative drug and administration of steroids to decrease further hypersensitivity reaction and IL-5 cytokine mediated eosinophil production. In hypereosinophilia-related stroke, steroids and immunosuppression may be beneficial, although no guidelines exist for the optimal duration of therapy.⁶ In addition, steroids may improve eosinophilic encephalopathy, although there are limited data given the rarity of this complication.⁹ Overall, results of this case suggest that central nervous system complications may arise with DRESS, including encephalopathy and stroke, and may be related to hypereosinophilia. Physicians should be aware of this potential complication of eosinophilia.

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