Letter to the Editor

Drug Rash With Eosinophilia and Systemic Symptoms (DRESS Syndrome)

To the Editor:

Drug rash with eosinophilia and systemic symptoms (DRESS syndrome), also known as drug-induced hypersensitivity syndrome, is a severe condition caused by drug treatment, most frequently anticonvulsants. It is defined by the presence of a cutaneous drug eruption in combination with hematologic abnormalities, mainly hypereosinophilia or the presence of atypical lymphocytes and at least one of the following systemic findings: enlarged lymph nodes, abnormal liver function, renal impairment, or pulmonary or cardiac infiltrates.[1] Ziprasidone, an atypical antipsychotic drug, is a commonly prescribed medication for the treatment of many psychiatric conditions; its association with DRESS syndrome is rare. An etiologic role of herpesviruses in the development of this syndrome also has been suggested.[2-4] We describe a patient who developed fever, rash, and toxic hepatitis, as well as reactivation of Epstein-Barr virus (EBV), approximately 14 days after starting ziprasidone.

Case Report

A 27-year-old black woman with a history of bipolar disorder was admitted to a psychiatric hospital for acute management of her condition. At the time of admission, she was taking valproic acid and mirtazapine with unknown compliance. She was subsequently started on ziprasidone and was discharged 2 weeks later on a psychiatric regimen of ziprasidone 80 mg twice daily and valproic acid 500 mg 3 times daily. Additional medications started at the time of discharge included trimethoprim-sulfamethoxazole, amoxicillin, and clindamycin for a suspected upper respiratory tract infection.

Four days after discharge from the psychiatric hospital (approximately 2 weeks following initiation of ziprasidone and 4 days after starting the previously mentioned antibiotics), the patient presented to the emergency department with pharyngitis, odynophagia, left-sided facial swelling, bilateral upper extremity rash of several days' duration, and a fever of up to 40.5°C. She was admitted to the intensive care unit with high-grade fever, hypotension, severe tachycardia, and altered mental status. The psychiatry department was consulted and haloperidol was initiated for delirium. Valproic acid and ziprasidone were discontinued on hospital day 2. The patient's laboratory values were consistent with a leukemoid-type response with a white blood cell count of up to 45,000 (reference range, 4500–11,000/μL), eosinophilia up to 19% (reference range, 2.7%), lymphocytosis 53% (reference range, 34%), and of neutrophil bands of 42% (reference range, ≤3%). Alkaline phosphatase peaked at 812 U/L (reference range, 30–120 U/L). Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) peaked at 688 U/L (reference range, 10–40 U/L) and 598 U/L (reference range, 10–30 U/L), respectively. Total bilirubin was 2.6 mg/dL (reference range, 0.3–1.2 mg/dL) and direct bilirubin was 1.6 mg/dL (reference range, 0.1–0.3 mg/dL). Blood, urine, and cerebrospinal fluid culture did not reveal any abnormalities. Trimethoprim-sulfamethoxazole, amoxicillin, and clindamycin were all stopped; ceftriaxone, vancomycin, and piperacillin-tazobactam were all initiated at varying times during her stay with minimal improvement in symptoms.

The patient underwent an extensive viral workup including serologies for human immunodeficiency virus and hepatitis A, B, and C, all negative. Cytomegalovirus polymerase chain reaction (PCR) was undetectable. Initial EBV PCR showed 650 copies and repeat analysis 4 days later demonstrated 3800 copies (positive, >300 copies). Epstein-Barr virus nuclear antigen was positive, indicating prior infection. Her rapid strep throat monospot, enterovirus RNA, herpes simplex virus DNA, and gonorrhea and chlamydia testing did not reveal any abnormalities. Ehrlichia antibodies, Rocky Mountain spotted fever antibodies, and toxoplasmosis immunoglobulins IgG and IgM also were obtained and were negative. Right upper quadrant abdominal ultrasound did not reveal any abnormalities. Computed tomography of the chest, abdomen, and pelvis showed borderline hepatomegaly. Flow cytometry demonstrated a distinct population of cytotoxic T cells consistent with reactive lymphocytosis. Although she did not have typical symptoms and did not meet criteria for

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hemophagocytic syndrome, she was still presumed to have EBV reactivation of unclear etiology. On hospital day 5, the patient was subsequently placed on a low dose of prednisone 20 mg daily. Higher doses of steroids were not started during this admission. Symptoms improved and the patient was discharged after 10 days. Her discharge medications included ziprasidone 40 mg twice daily for 2 days followed by 80 mg twice daily, prednisone 20 mg daily, and zolpidem as needed for insomnia. The time of discharge was the first time ziprasidone was reintroduced since stopping it 10 days prior.

The patient returned to the hospital 2 days later with progressive fevers and worsening malaise. She was found to have markedly elevated liver function tests with ALT peaking at 2061 U/L and AST of 3542 U/L. Additionally, she had elevated total bilirubin up to 11.5 mg/dL and coagulopathy, all consistent with acute hepatitis. She underwent a liver biopsy that revealed bridging hepatic necrosis. The patient was deemed a potential candidate for liver transplantation and evaluation was initiated.

The dermatology service was consulted on hospital day 2 to evaluate the patient's skin findings. On examination, she had minimal erythema with scant scale circumferentially lining her neck and perioral regions and rare hypopigmented macules with fine xerotic scale overlying her trunk and extremities. In light of her constellation of systemic manifestations including fever, rash, transaminitis, and lymphadenopathy, it was presumed that her presentation was consistent with a hypersensitivity reaction to ziprasidone. Furthermore, her negative workup and the chronological appearance of illness following initiation of ziprasidone supported the diagnosis. Ziprasidone was discontinued and oral prednisone 60 mg daily was started 2 days later. The patient's clinical appearance improved dramatically and her transaminitis began to resolve. Her ALT was 780 U/L and her AST was 231 U/L at the time of discharge, 7 days after the ziprasidone was discontinued and 5 days after prednisone was initiated. She was discharged on a prednisone taper and risperidone 1 mg twice daily was substituted for ziprasidone for the management of her bipolar disorder per the recommendation of the hospital's psychiatry consultation service.

Comment

Drug-induced hypersensitivity syndrome most commonly follows exposure to anticonvulsants. It is estimated that this potentially fatal drug reaction occurs every 1 in 1000 to 1 in 10,000 exposures.[5] In a study of 31 patients with anticonvulsant hypersensitivity syndrome, 15 cases (48.38%) were attributed to carbamazepine, 11 cases (35.48%) to phenytoin, 3 cases (9.68%) to lamotrigine, and 2 cases (6.45%) to concomitant treatment with lamotrigine and valproic acid.[6] According to a PubMed search of articles indexed for MEDLINE using the terms *hypersensitivity syndrome* and *antipsychotics*, there have only been 2 cases of hypersensitivity syndromes associated with atypical antipsychotics. In another case involving ziprasidone, an elderly patient developed a severe total body skin eruption with fever and accompanying toxic hepatitis 11 days after initiation of the medication for aged psychosis.[7] The other documented case of antipsychotic-induced hypersensitivity syndrome involved olanzapine. In this case, the patient developed a severe skin eruption, fever, and transaminitis 60 days after initiation of olanzapine for paranoid schizophrenia.[8] Our patient presented to the emergency department 14 days after initiation of ziprasidone, chronologically consistent with prior reports of hypersensitivity.

Fever, malaise, pharyngitis, and cervical lymphadenopathy are presenting symptoms of DRESS syndrome and frequently begin 1 to 8 weeks after initiation of a drug. Rash normally follows and can range from a simple exanthem to toxic epidermal necrolysis. Internal organ involvement generally involves the liver. Our patient's constellation of symptoms and course were consistent with the natural progression of DRESS syndrome. Although she was taking both ziprasidone and valproic acid before her initial presentation to our emergency department, she had been maintained on valproic acid for many months previously without any adverse reactions and had been started on ziprasidone only 2 weeks prior to admission.

It also is now recognized that DRESS syndrome can be associated with reactivation of human herpesviruses, most commonly secondary to human herpesvirus 6.[2] Reactivation of cytomegalovirus or EBV also has been reported.[3,4] Our patient's Epstein-Barr virus nuclear antigen was positive, indicating prior infection with EBV. In addition, EBV PCR results were as high as 3800 copies in the blood, suggesting that EBV reactivation played a role in our patient's symptoms. In our case, it was initially presumed that the patient's symptoms were secondary to reactivation of EBV alone. However, worsening of her symptoms upon rechallenge with ziprasidone as a single agent and the chronological duration of treatment strongly support the diagnosis of ziprasidone-induced DRESS syndrome. The improvement of her symptoms approximately 1 week after stopping ziprasidone following each admission further substantiated this diagnosis.

The pathophysiology of DRESS syndrome is poorly understood. The key to managing this potentially fatal reaction is early recognition of the syndrome and immediate discontinuation of the offending

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agent. Systemic steroids may help in management. This syndrome may mimic many different pathologic processes. As a result of many nonspecific manifestations, DRESS syndrome may be vastly underreported. Patients on antipsychotic medications also may be treated with anticonvulsants, which may make elucidation of the etiology of the disease even more difficult. Similar phenomena such as anticonvulsant hypersensitivity syndrome and pseudolymphoma may mimic this condition, further obscuring the diagnosis. Although relatively uncommon, a variety of drugs have been implicated in hypersensitivity and it is likely that the incidence of antipsychotic-induced DRESS syndrome is greater than once thought.

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The authors report no conflict of interest.

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