JPPT

Case Report

Drug Reaction With Eosinophilia and Systemic Symptoms (DRESS) in an Adolescent Treated With Lamotrigine

Almari Ginory, DO,[1] Michelle Chaney-Catchpole, MD, MScPH,[1] Julie M. Demetree, MD,[1] Laura M. Mayol Sabatier, MD,[1,2] and Mathew Nguyen, MD [1,2]

[1]Department of Psychiatry, University of Florida, Gainesville, Florida, and [2]Division of Child and Adolescent Psychiatry, Department of Psychiatry, University of Florida, Gainesville, Florida

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a hypersensitivity syndrome most commonly associated with antiepileptic agents, allopurinol, and sulfonamides. It is a severe adverse reaction associated with fever, rash, eosinophilia, lymphadenopathy, and internal organ involvement. We present the case of a 17-year-old Caucasian female with bipolar disorder type II and posttraumatic stress disorder treated with lamotrigine for a non-Food and Drug Administration-approved indication that developed DRESS syndrome at an initial dose higher than that recommended. Her symptoms were atypical in that she developed a rash with influenza-like symptoms that resolved after discontinuation of lamotrigine and returned 8 days later. She was hospitalized because of elevated liver enzymes and treated with corticosteroids. In patients presenting with rash and systemic symptoms, DRESS syndrome should be considered and treated appropriately to reduce mortality, which can be as high as 10%. Treatment includes withdrawal of the offending agent and corticosteroids.

INDEX TERMS anticonvulsants, bipolar disorder, drug eruptions

J Pediatr Pharmacol Ther 2013;18(3):236–240

INTRODUCTION

Lamotrigine is an aromatic antiepileptic medication approved for the treatment of seizures in children and adults, as well as for bipolar type I disorder in adults.[1] Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, also referred to as drug-induced hypersensitivity syndrome, is a severe, potentially life threatening, adverse reaction most commonly associated with antiepileptic medications, sulfonamides, and allopurinol.[2] Symptoms of DRESS syndrome include fever, rash, eosinophilia, lymphadenopathy, and internal organ involvement.[3] Compared to adults, children have an increased risk of developing a serious rash associated with lamotrigine.[4] Several case reports describe children who developed DRESS syndrome after treatment with lamotrigine for epilepsy.[5,6] Most of those children were receiving concomitant valproic acid, which is also a risk factor for development of dermatologic reactions associated with lamotrigine. Herein, we present the case of a 17-year-old female with the diagnosis of bipolar II disorder and posttraumatic stress disorder (PTSD) treated with lamotrigine monotherapy, who was admitted to our hospital for treatment of DRESS syndrome.

CASE REPORT

The patient was a 17-year-old, 62-kg Caucasian female initially admitted to an inpatient psychiatric hospital due to outbursts of anger and violent threats toward her family members. During this hospitalization period, bipolar II disorder and PTSD were diagnosed. She had no known medical comorbidities. The patient reported periods of 5 to 10 days during which where she would have increased irritability and decreased need for sleep, flight of ideas, and an increased rate of speech. The episodes were never severe enough to cause marked impairment in social functioning, and there were no psychotic features. Afterward, the patient stated she would "crash" and feel very depressed and hopeless. She would also

have 2- to 3-week periods of decreased energy, decreased appetite, anhedonia, depressed mood, and suicidal ideations without a plan. The patient had been sexually and physically abused as a child. She admitted to experiencing nightmares and flashbacks about these events. She also reported persistent avoidance of stimuli associated with the trauma as well as persistent symptoms of increased arousal, including exaggerated startle response and irritability/outbursts of anger. Prior to admission, the patient was treated with fluoxetine, sertraline, citalopram, venlafaxine, and lithium without any noticeable benefit. Patient was started on lamotrigine, 25 mg twice daily, as monotherapy and discharged with the same dose. She was not prescribed any other medications and denied taking any over-the-counter medications or herbal products.

Three weeks after starting lamotrigine, the patient developed a rash and general influenza-like symptoms. Her mother was concerned this was an adverse drug reaction and independently discontinued lamotrigine. The rash resolved within 3 days. Approximately 8 days later, the patient developed a new onset of diffuse rash, fever to a maximum temperature of 103°F, abdominal upset, and generalized fatigue. The rash started on the patient's face and upper chest. It appeared as diffuse, blanchable, erythematous papules that coalesced to form larger plaques on the upper chest, back, upper extremities, and lower extremities. The patient had mild erythema of the palms with few scattered petechiae. She had dry mucosa with fissuring on the lips and also had facial edema with erythematous patches on bilateral cheeks. Significant bilateral cervical lymphadenopathy was also noted.

The patient was admitted to our hospital for evaluation of the above-described symptoms approximately 5 weeks after initiation of lamotrigine. Upon admission, she had elevated liver function tests (aspartate aminotransferase [AST], 2057 U/L; alanine aminotransferase [ALT], 2076 U/L; alkaline phosphatase [Alk Phos], 455 U/L; total bilirubin, 6.5 mg/dL; direct bilirubin, 6.1 mg/dL; and albumin, 3.2 g/dL). Ammonia concentration on admission was 157 mmol/L. Toxicology and infectious screen results were negative for antinuclear antibody, blood culture, and hepatitis A, B, and C virus and chlamydia/mycoplasma infections. Her absolute eosinophil count was elevated at $0.85 \times 10^9 L^{-1.}$ On computed tomography scans of the abdomen, she was found to have a distended gallbladder with possible cholelithiasis, splenomegaly, and retroperitoneal adenopathy. She was diagnosed with DRESS syndrome based on the above-described symptoms and the history of treatment with lamotrigine. The scoring system for classifying DRESS is outlined in the Table.[6] Based on this scale, the patient had a score of 6, which is indicative of a definite case of DRESS syndrome.

Treatment for her symptoms included a regimen of broad-spectrum antibiotics and vancomycin to cover for cholangitis, which was causing or aggravating the transaminitis. She was treated with lactulose for her elevated ammonia, which trended downward to 102 mmol/L. The patient was treated with five doses of methylprednisolone, 125 mg intravenous (IV) daily. She responded to this treatment, and her liver enzymes trended down, but she subsequently developed steroid-induced hyperglycemia that required treatment with insulin. On the day of discharge, AST had trended down to 121 U/L, ALT to 458 U/L, and Alk Phos to 192 U/L, and total bilirubin had trended down to 5.4 mg/dL. The patient was discharged on a 6-week regimen of prednisone taper and insulin glargine, 20 units subcutaneous nightly, for treatment of steroid-induced hyperglycemia.

Psychotropic medications were not initiated during her hospital stay because of the severity of her medical symptoms and stability of her psychiatric symptoms. We recommended that she avoid aromatic antiepileptic medications in the future for control of her mood as she might be at increased risk of similar hypersensitivity syndromes. She was advised to follow-up with her outpatient psychiatrist once her liver enzymes normalized, with the recommendation to start a US Food and Drug Administration (FDA)-approved treatment for bipolar disorder in adolescents.

DISCUSSION

DRESS syndrome was first described by Bocquet et al.[8] as a hypersensitivity reaction occurring within the first 2 months of initiation of drug treatment. Symptoms include diffuse maculopapular rash; fever; hematologic abnormalities such as atypical lymphocytes and eosinophilia; and lymphadenopathy and organ involvement.[8]

Table. Scoring System for Classifying DRESS Applied to the Patient*

Presentation: Symptom and Laboratory Findings	Result	Score
Fever ≥101.3°F	103°F	0
Lymphadenopathy	Yes	1
Eosinophils >0.7 × 10^9 L^{-1}	0.85 × 10^9 L^{-1}	1
Atypical lymphocytes	Yes	1
Skin rash		
Extent >50%	Unknown	0
Rash suggesting DRESS	Yes	1
Biopsy suggesting DRESS	Unknown	0
Organ Involvement		
Liver	Yes	1
Kidney	No	0
Lung	No	0
Muscle/heart	No	0
Pancreas	No	0
Other	No	0
Resolution ≥15 days	Yes	0
Evaluation of other potential causes		
Antinuclear antibody	Negative	
Blood culture	Negative	
HAV/HBV/HVC	Negative	
Chlamydia/Mycoplasma	Negative	
If none positive and ≥3 negative	Yes	1
Total score		6

HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus.

** Table based on reference 6.*

† *Final score of <2, no case; score 2-3, possible case; score 4-5, probable case; score >5 definite case. Range of total score is −4 to 9.*

Later studies have further elucidated symptoms and diagnostic scales. Additionally, the syndrome is now referred to as DRESS because of the variability of skin involvement.[9]

Diagnosis is at times difficult because of the variability of symptoms and organ involvement. The onset of symptoms is between 2 and 6 weeks, which is delayed compared to other adverse skin rashes.[3] The most common presenting symptoms are fever and diffuse maculopapular rash.[9] Other symptoms include lymphadenopathy, mucosal involvement, atypical lymphocytes, eosinophilia, and leukocytosis. Of note, eosinophilia, although part of the acronym, is present only in approximately 30% of cases.[9] The most common organ involved is the liver, with patients presenting with elevated liver enzymes, hepatitis, and jaundice.[2] Other visceral reactions that have been noted include pneumonitis and nephritis and, less commonly, pancreatitis.[10] Due to the variability of symptoms, Kardaum et al.[6] developed the European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) scoring system, which is outlined in the Table, to assist professional judgment in classifying suspected cases as no case, possible case, probable case, or definite case.[7]

DRESS syndrome associated with lamotrigine was found to have more severe rash, less eosinophilia, and less lymphadenopathy than symptoms resulting from other antiepileptic agents.[6] This patient's symptoms were atypical as she initially reported a rash and influenza-like symptoms, which improved after her mother discontinued the lamotrigine. She had suspended use of the medication for over a week when the rash returned along with a fever, generalized fatigue, and abdominal upset. Her RegiSCAR score was 6, which is indicative of a definite case of DRESS syndrome. To our knowledge this is the first report of this atypical symptom pattern.

DRESS is most commonly associated with sulfonamides, allopurinol, and antiepileptic medications.[11] Of the antiepileptic agents, most cases report involvement of carbamazepine, phenobarbital, and lamotrigine.[12] The estimated incidence of DRESS syndrome ranges from 1

case/1000 to 1 case/10,000 of those exposed to offending agents.[3] The exact pathophysiology of DRESS syndrome is unknown but is theorized to be the result of an immune reaction, abnormal metabolism, or activation of human herpes virus 6.[7] It is considered a delayed hypersensitivity, type IV, drug reaction mediated by T cells.[6]

Potential risk factors for the development of rash in patients treated with lamotrigine include coadministration with valproate, larger than recommended starting dose, and rapid dose escalation.[1] Incidence of rash is also greater in pediatric patients[1]; however, these have not been associated with increased risk of developing DRESS but should be considered when treating patients with lamotrigine.[10] Previous case reports of children with DRESS associated with lamotrigine have also described simultaneous treatment with other antiepileptic medicines such as valproic acid and phenytoin.[4,5] Our patient was receiving lamotrigine monotherapy when she developed symptoms but was treated at a larger than recommended starting dose which has been reported to increase the risk for nonserious dermatologic rash. She was also under the age of 18 and being treated for bipolar II disorder, for which lamotrigine is not indicated. Caution should be used with prescribing medications, such as lamotrigine, in patients with risk factors for adverse reactions, such as age, for non-FDA-approved indications. Caution should also be used when prescribing other aromatic antiepileptic medications, such as carbamazepine, phenytoin, and phenobarbital, as there is a risk of cross-sensitivity and increased risk of future rash among these medications.[13] Of note, this cross-sensitivity has not been found between aromatic and nonaromatic antiepileptic medications.[13]

Early diagnosis and treatment are crucial as this syndrome is associated with a 10% mortality rate.[10] Treatment includes early withdrawal of the offending agent and supportive care.[9] There is no standard treatment for DRESS syndrome, but case reports show improvement in symptoms in those treated with corticosteroids, especially in those with internal organ involvement.[2] In one case report, symptoms improved more rapidly in a patient treated with pulse methylprednisolone plus oral methylprednisolone than therapy described in prior reports.[14] Laboratory data should be followed closely for improvement in laboratory abnormalities.

CONCLUSIONS

In conclusion, DRESS syndrome is a severe adverse drug reaction associated with several medications, including lamotrigine. Due to the large variability of symptoms and 10% mortality rate, healthcare providers should have a high index of suspicion for this syndrome in patients treated with these agents, presenting with symptoms of fever, rash, lymphadenopathy, hematologic abnormalities, and organ involvement. If the rash resolves and subsequently reappears even after discontinuation of the offending medication, DRESS syndrome should still be in the differential diagnosis and adequately treated, as was the case with this patient.

DISCLOSURES The authors declare no conflicts or financial interests in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

ABBREVIATIONS ALT, alanine aminotransferase; Alk Phos, alkaline phosphatase; AST, aspartate aminotransferase; DRESS, drug reaction with eosinophilia and systemic symptoms; FDA, Food and Drug Administration; IV, intravenous; PTSD, post-traumatic stress disorder.

CORRESPONDENCE Almari Ginory, DO, PO Box 100256, Gainesville, FL 32610, email: ginory@ufl.edu

REFERENCES

1. Food and Drug Administration. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020241s050,020764s043,022251s013lbl.pdf. Accessed May 1, 2013.
2. Chiou CC, Yang LC, Hung S, et al. Clinicopathological features and prognosis of drug rash with eosinophilia and systemic symptoms: a study of 30 cases in Taiwan. *J Eur Acad Dermatol Venereol*. 2008;22(9):1044-1049.
3. Amante MF, Filippini AV, Cejas N, et al. Dress syndrome and fulminant hepatic failure induced by lamotrigine. *Ann Hepatol*. 2009; 8(1):75-77.
4. Schlienger RG, Knowles SR, Shear NH. Lamotrigine-associated anticonvulsant hypersensitivity syndrome. *Neurology*. 1998;51(4):1172-1176.

5. Chattergoon DS, McGuigan MA, Koren G, et al. Multiorgan dysfunction and disseminated intravascular coagulopathy in children receiving lamotrigine and valproic acid. *Neurology*. 1997;49(5):1442-1424.
6. Kardaum SH, Sidoroff A, Valeyrie-Allanore L, et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? *Br J Dermatol*. 2007;156(3):609-611.
7. Bocquet H, Bagot M, Roujeau JC. Drug-induced pseudolymphoma and drug hypersensitivity syndrome (drug rash with eosinophilia and systemic symptoms: DRESS). *Semin Cutan Med Surg*. 1996;15(4):250-257.
8. Criado PR, Criado RFJ, Avancini JM, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS): a review of current concepts. *An Bras Dermatol*. 2012; 87(3):435-449.
9. Roquin G, Peres M, Lerolle N, et al. First report of lamotrigine-induced drug rash with eosinophilia and systemic symptoms syndrome with pancreatitis. *Ann Pharmacother*. 2010;44(12):1998-2000.
10. Fleming P, Marik PE. The DRESS syndrome: the great clinical mimicker. *Pharmacotherapy*. 2011;31(3):332.
11. Cacoub P, Musette P, Descamps V, et al. The DRESS syndrome: a literature review. *Am J Med*. 2011;124(7):588-597.
12. Pereira N, Piquioni P, Kochen S, et al. Risk factors associated with DRESS syndrome produced by aromatic and non-aromatic antipiletic drugs. *Eur J Clin Pharmacol*. 2011;67(5):463-470.
13. Hyson C, Sadler M. Cross sensitivity of skin rashes with antiepileptic drugs. *Can J Neurol Sci*. 1997,24: 245-249.
14. Kocaoglu C, Cilasun C, Solak ES, Kurtipek GS, Arslan S. Successful treatment of antiepileptic drug-induced DRESS syndrome with pulse methylprednisolone. *Case Rep Pediatr*. 2013;2013:928910.