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Hypersensitivity Syndrome Induced by Anticonvulsants: Possible Cross-Reactivity Between Carbamazepine and Lamotrigine

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A 14-year-old male presents with erythroderma and fever 44 days after carbamazepine intake. Laboratory exams show eosinophilia and elevated liver enzymes, and thoracic imaging reveals interstitial pneumonitis. All symptoms disappear after carbamazepine withdrawal. A patch test to carbamazepine performed 6 weeks after recovery is positive. About 8 months later, the patient exhibits the same clinical and biological picture 52 days after lamotrigine intake. Lamotrigine is stopped and all symptoms disappear. A patch test to

LMG is positive. This case illustrates a possible cross-reactivity between carbamazepine and lamotrigine, which are aromatic and nonaromatic anticonvulsants, respectively.

Keywords: DRESS; carbamazepine; lamotrigine; cross-reactivity

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Hypersensitivity syndrome is an idiosyncratic, severe drug reaction. Its clinical manifestations include rash, fever, the involvement of multiple visceral organs, and some hematological abnormalities such as eosinophilia.¹ Bocquet et al² introduced the term *DRESS* (drug rash, eosinophilia, and systemic symptoms) *syndrome* to characterize such a drug hypersensitivity reaction and to distinguish it from drug-induced pseudolymphoma. Numerous drugs such as sulfonamides, nevirapine, allopurinol, and isoniazid have been reported to cause DRESS syndrome.³ However, anticonvulsants, especially

aromatic ones such as phenytoin, carbamazepine (CBZ), phenobarbitone, and primidone, are still the principal drugs that elicit this syndrome.⁴ Nonaromatic anticonvulsants such as lamotrigine (LMG), a relatively new anticonvulsant, are rarely reported to induce DRESS syndrome.⁵ Cross-reactivity among the aromatic anticonvulsants frequently occurs (40%-80% of patients)⁶; however, cross-reactivity between aromatic and nonaromatic anticonvulsants has, to the best of our knowledge, not been described in the medical literature. We present here a case of a CBZ-induced DRESS syndrome that recurred after subsequent administration of LMG, and we show the usefulness of the patch test in diagnosing hypersensitivity to both drugs.

CASE REPORT

A 14-year-old male presented with erythroderma, facial edema, sore throat, and fever. Prior to this, the patient had taken CBZ for 44 days for absence epilepsy. On admission his temperature was 40°C, blood pressure 100/60 mm Hg, pulse 88 beats/min,

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and respiratory rate 14 breaths/min. On physical examination, a generalized, diffuse, maculopapular, erythematous, pruritic rash was noted over the face, trunk, and extremities with marked facial edema. The laboratory findings showed an abnormal white cell count ($23 \times 10^9/L$, 15% eosinophils) with atypical lymphocytes and liver dysfunction with an aspartate aminotransferase (AST) level of 210 IU/L (normal 7-38 IU/L), an alanine aminotransferase (ALT) level of 193 IU/L (normal 4-40 IU/L), and a lactate dehydrogenase (LDH) level of 514 (normal 190-430 IU/L). The platelet count, international normalized ratio, serum levels of immunoglobulins, and renal function were conversely normal. Thoracic imaging revealed interstitial pneumonitis. Serological tests for viral infections including cytomegalovirus, Epstein-Barr virus, hepatitis B and C, and human immunodeficiency virus were all negative. CBZ was then discontinued, and cetirizine was administered. The HHV6 serological test performed on day 21 after symptoms onset was negative. About 1 month after CBZ withdrawal, the skin eruption, fever, lymph node swelling, liver dysfunction, and eosinophilia were completely relieved. Six weeks after complete recovery, a patch test to CBZ (5% petrolatum) was performed and was positive at the 48-hour reading (Figure 1). About 6 months later, the patient was treated with LMG for his epilepsy. On day 52 of the LMG course, he presented fever ($39.2^\circ C$), erythroderma, and lymph node swelling with leukocytosis ($13.1 \times 10^9/L$), eosinophilia (12%), elevated liver enzymes (AST 143 and ALT 154) and LDH (479), and interstitial pneumonitis. LMG-induced DRESS syndrome was then suspected, and the drug was stopped. Approximately 20 days later, the clinical and biological symptoms disappeared. The HHV6 serological test performed on day 21 after symptoms onset was negative. A patch test to LMG (5% petrolatum) performed 6 weeks after recovery was positive at the 48-hour reading (Figure 2).

DISCUSSION

This case report describes a patient who developed a CBZ-induced DRESS syndrome that recurred after an LMG course. Indeed, a clear temporal relationship was observed between CBZ and LMG administration and symptom onset (44 and 52 days respectively, typically 2-6 weeks),¹ the remission of symptoms after CBZ and LMG withdrawal, and the positive results of CBZ and LMG patch tests. Based on the Naranjo algorithm,⁷ it is probable that the



Figure 1. Positive patch test to carbamazepine (48-hour reading).



Figure 2. Positive patch test to lamotrigine (48-hour reading).

first episode of the systemic reaction was due to CBZ and the second to LMG. DRESS syndrome is a severe idiosyncratic drug reaction, linked to a high mortality rate (10%).⁸ Its clinical picture includes fever, morbiliform eruption, lymphadenopathy, pneumonitis, liver and renal dysfunctions, and hematological abnormalities such as eosinophilia and atypical lymphocytosis. Except for renal dysfunction, all these features were observed in our patient during both episodes of drug reaction. It has been reported that DRESS syndrome could be associated with human

herpes virus (HHV6) reactivation.⁹ We recently described a CBZ-induced DRESS syndrome associated with an HHV6 primary infection.¹⁰ Nevertheless, in our patient HHV6 serological tests performed in the course of both episodes of DRESS syndrome were negative. Several drugs including sulphonamides and allopurinol have been associated with an increased risk of inducing such a syndrome, but the aromatic anticonvulsants are still the main drugs implicated in eliciting DRESS syndrome. It has been suggested that a defect in the epoxide hydroxylases, which induces the accumulation of toxic metabolites of CBZ, may lead to cell death or contribute to the formation of antigens, triggering the immune reaction involved in DRESS syndrome.¹ However, in our patient the patch test was positive to CBZ, and it can be argued that the drug reaction may be caused by CBZ itself and not its reactive metabolite. Recently, some cases of DRESS syndrome induced by LMG, a nonaromatic anticonvulsant, have been described in the literature.¹¹⁻¹³ However, in none of these reports was the causality confirmed by patch test. In our patient, the patch test performed for LMG was positive at the 48-hour reading. It has been thought that the hypersensitivity reactions are an immunological response to metabolically generated drug-protein adducts,⁵ but recent data demonstrate a lack of evidence of significant reactive metabolite formation in the skin, so the drug reactions caused by LMG may be caused by the parent drug instead of a reactive metabolite.^{14,15} As the patch test to LMG performed in our patient was positive, we can confirm this hypothesis.

In our patient, there was a significant cross-reactivity between CBZ and LMG despite the difference in the chemical structures of the 2 drugs (Figure 3). Indeed, cross-reactivity has been widely described among the aromatic anticonvulsants and occurs at a rate as high as 80%.⁶ This finding has been explained by the fact that these drugs are metabolized into structurally similar reactive intermediates, such as toxic arene oxides. These intermediates may bind covalently to cellular macromolecules, directly causing cell damage or initiating immune responses. As mentioned above, both episodes of hypersensitivity reaction exhibited by our patient are thought to be elicited by CBZ and LMG themselves and not by intermediates, suggesting a cell-mediated cross-reactivity.¹⁶ However, it cannot be ruled out that LMG-induced DRESS syndrome resulted from an independent second reaction. Indeed, the time lag between start of drug intake and the DRESS event, which is supposed to be shorter in case of cross reactivity, was longer for LMG (52 days vs 44 days for CBZ).

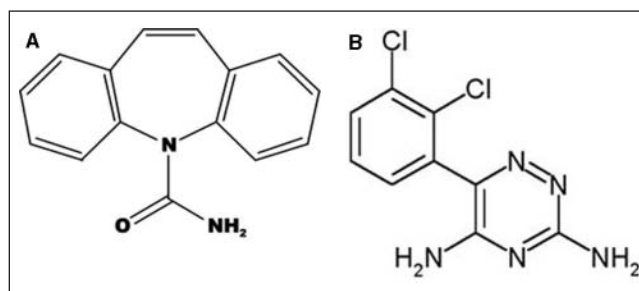


Figure 3. (A) Chemical structure of carbamazepine. (B) Chemical structure of lamotrigine.

Through this report, we add to the medical literature a new case of DRESS syndrome induced by LMG and point out the usefulness of the patch test in the diagnosis of this drug reaction. We also describe for the first time the possibility of cross-reactivity between aromatic and nonaromatic anticonvulsant drugs.

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REFERENCES

- Sullivan JR, Shear NH. The drug hypersensitivity syndrome. What is the pathogenesis? *Arch Dermatol*. 2001;137:357-363.
- 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;15:250-257.
- Begon E, Roujeau JC. Drug hypersensitivity syndrome: DRESS (drug reaction with eosinophilia and systemic symptoms). *Ann Dermatol Venereol*. 2004;131:293-297.
- Shear NH, Spielberg SP. Anticonvulsant hypersensitivity syndrome in vitro assessment of risk. *Clin Invest*. 1988;82:1826-1832.
- Veyrac G, Marcade G, Chiffolleau A, Bourin M, Joliet P. Characteristics of hypersensitivity syndrome to lamotrigine: review of one case reported in the Regional Center of Pharmacovigilance of Nantes. *Therapie*. 2002;57:289-296.
- Knowles SR, Shapiro LE, Shear NH. Anticonvulsant hypersensitivity syndrome: incidence, prevention and management. *Drug Saf*. 1999;21:489-501.
- Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30:239-245.
- Allam JP, Paus T, Reichel C, Bieber T, Novak N. DRESS syndrome associated with carbamazepine and phenytoin. *Eur J Dermatol*. 2004;14:339-342.
- Descamps V, Bouscarat F, Laglenne S, et al. Human herpesvirus 6 infection associated with anticonvulsant hypersensitivity syndrome

and reactive haemophagocytic syndrome. *Br J Dermatol.* 1997;137: 605-608.

10. Aouam K, Bel Hadj Ali H, Youssef M, et al. Carbamazepine-induced DRESS and HHV6 primary infection: The importance of skin tests. *Epilepsia.* 2008 [E-pub ahead of print]

11. Schaub N, Bircher AJ. Severe hypersensitivity syndrome to lamotrigine confirmed by lymphocyte stimulation in vitro. *Allergy.* 2000;55:191-193.

12. Karande S, Gogtay NJ, Kanchan S, Kshirsagar NA. Anti-convulsant hypersensitivity syndrome to lamotrigine confirmed by lymphocyte stimulation in vitro. *Indian J Med Sci.* 2006;60:59-63.

13. Blondin NA, Zahedi S, Hale MS. A case of lamotrigine-associated anticonvulsant hypersensitivity syndrome. *Prim Care Companion J Clin Psychiatry.* 2008;10:249-250.

14. Maggs JL, Naisbitt DJ, Tettey JN, Pirmohamed M, Park BK. Metabolism of lamotrigine to a reactive arene oxide intermediate. *Chem Res Toxicol.* 2000;13:1075-1081.

15. Lu W, Uetrecht JP. Possible bioactivation pathways of lamotrigine. *Drug Metab Dispos.* 2007;35:1050-1056.

16. Romano A, Guéant-Rodriguez RM, Viola M, Gaeta F, Caruso C, Guéant JL. Cross-reactivity among drugs: clinical problems. *Toxicology.* 2005;209:169-179.