Lamotrigine-induced DRESS with purpuric lesions in the oral mucosa

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INTRODUCTION

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a potentially life-threatening, severe cutaneous adverse drug reaction characterized by a maculopapular skin rash with fever, hematologic abnormalities (leukocytosis, eosinophilia, and/or atypical lymphocytosis), and multiorgan involvement.[1] Aromatic anticonvulsants (carbamazepine, phenytoin, phenobarbital) and sulfonamides are the most commonly reported causes of this condition.[1] Lamotrigine is an aromatic anticonvulsant and has been increasingly reported in association with DRESS in recent years. Lamotrigine-induced DRESS associated with purpuric lesions is extremely rare. To our knowledge, lamotrigine-induced DRESS with purpuric lesions in the oral mucosa has not been described.

CASE REPORT

A 31-year-old woman presented to our department with complaints of widespread rash, fever, and fatigue. She had been using valproic acid (750 mg/d) for years to control epileptic seizures. Lamotrigine had been started as add-on therapy with a dose titration (12.5 mg/d first 2 weeks and 25 mg/d in the third week), and after the third week, her complaints started. The patient had no history of any further drug use.

On dermatologic examination, in addition to generalized maculopapular eruption, there were purpuric lesions on the torso (Fig 1) and both upper thighs (Fig 2) and prominent facial and periorbital edema and cheilitis. Oral mucosa examination found purpuric lesions on the hard palate (Fig 3) and erythematous tonsils. Her fever was 38.3°C and bilateral inguinal lymphadenopathy was present. In laboratory tests, leukocytosis (11.600/mm^3), neutrophilia (10.170/mm^3), lymphopenia (720/mm^3), elevation in liver function values (alanine aminotransferase, 95 U/L; aspartate transaminase, 56 U/L), and deterioration of thyroid function tests (thyroid-stimulating hormone, 0.39 μIU/mL; free triiodothyronine, 2.24 pg/mL) were detected. There was no eosinophilia. Peripheral blood smear was normal. The patient was hospitalized, and a punch biopsy specimen was obtained from maculopapular eruption located on the right subcostal area. Histopathologic examination found spongiosis, exocytosis of lymphocytes, and a perivascular infiltrate of lymphocytes and eosinophils in papillary dermis (Fig 4). Lamotrigine-induced DRESS was diagnosed with typical history and clinical and laboratory findings. Lamotrigine was discontinued, and systemic methylprednisolone (1 mg/kg/d, intravenous) and topical methylprednisolone aseponate treatment were initiated. On the follow-up thyroid-stimulating hormone level increased (from 0.39 to 0.78 μIU/mL), whereas free triiodothyronine (from 2.24 to 1.61 pg/mL) and free thyroxine (from 0.95 to 0.87 pg/mL) decreased, but antithyroid peroxidase and antithyroglobulin antibodies remained negative.

Abbreviation used:

DRESS: drug reaction with eosinophilia and systemic symptoms

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Fig 1. Maculopapular eruption and purpuric lesions on the torso.

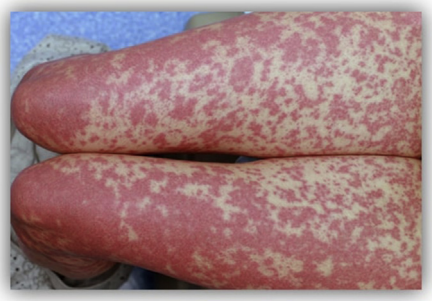


Fig 2. Maculopapular and purpuric lesions on the upper thighs.



Fig 3. Purpuric lesions on the hard palate.

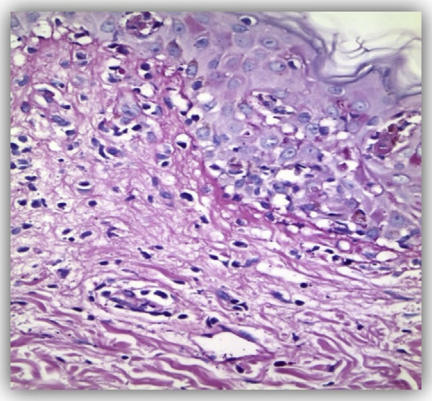


Fig 4. Spongiosis, exocytosis of lymphocytes, and a perivascular infiltrate of lymphocytes and eosinophils in the papillary dermis.

The patient was referred to the endocrinology clinic, and thyroid function abnormality was assessed as euthyroid sick syndrome. The rest of the physical examination, routine laboratory investigations, and echocardiography were normal. With the treatment, the clinical and systemic symptoms rapidly improved in 2 weeks, and the patient was discharged.

DISCUSSION

Lamotrigine is an aromatic anticonvulsant drug that is hepatically eliminated through glucuronidation by the uridine diphosphate glucuronosyl transferase enzyme.[2] Valproate is a broad spectrum inhibitor of the uridine diphosphate glucuronosyl transferase enzyme.[3] When valproate is used in combination with lamotrigine, because of the inhibition of elimination, the half-life of lamotrigine prolongs and its serum levels elevate.[4] Risk factors for severe cutaneous adverse effects caused by lamotrigine include rapid dose titration, concurrent valproic acid administration, prior history of an anticonvulsant-associated rash, female sex and age less than 13 years.[5] Interestingly, although lamotrigine was started at a low dose and was slowly increased per the International Core Prescribing guidelines for lamotrigine as monotherapy and add-on therapy in adults, DRESS developed in our case. This finding may be caused by altered drug metabolism, complex immunologic mechanisms, and genetic factors. Verneuil et al[6] identified endothelial cell apoptosis in skin microvessels of 4 different types of T-lymphocyte—mediated drug-induced eruptions (DRESS, Stevens-Johnson syndrome/toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and drug maculopapular exanthema). In DRESS cases, apoptotic endothelial cell numbers were found to be significantly related to skin lesion extent greater than 60%, the presence of purpura, and liver and kidney involvement.[6] Valproate can affect the metabolism of lamotrigine and facilitate the conversion of lamotrigine into haptens to induce T lymphocytes indirectly. As a result, when used with valproic acid, it may become easier for lamotrigine to cause purpuric lesions even

when used at low doses. In addition, some genetic factors may facilitate purpura formation.

In lamotrigine-induced DRESS, unlike the findings triggered by other antiepileptics, the incidence of severe cutaneous adverse effects tends to be high, whereas the frequency of eosinophilia and lymphadenopathy tends to be low.[7] In our case, cutaneous findings were severe, and there was no eosinophilia, consistent with previous findings.

Previously reported 2 lamotrigine-induced DRESS cases[8,9] associated with purpura differ from our case in terms of the duration of lamotrigine use and the location of the lesions. In the first case,[8] purpura developed after 23 weeks of lamotrigine use and was located on the buttocks, knees, and ankles. In the second case,[9] purpura developed on the legs and ankles after 16 weeks of lamotrigine use. Long-term use of lamotrigine and localization of the purpura to the lower extremities showed a similarity in both cases. However, in our case, the purpura appeared only after 3 weeks of lamotrigine use and showed widespread distribution. In the second case,[9] the prolonged presentation of purpura may be caused by the concomitant use of phenobarbital and carbamazepine, which lower serum lamotrigine level by inducing its metabolizing enzyme. In contrast, in our case, valproic acid, which is an enzyme inhibitor, was used in combination with lamotrigine, and the process of purpura formation was thought to be accelerated due to the increase of serum lamotrigine levels. In light of this potential pathophysiologic mechanism, we speculate that purpura is likely to appear at different times in association with the effects of concomitant medications on lamotrigine metabolism and its levels.[8]

This is the first case report, to our knowledge, of lamotrigine-induced DRESS associated with purpuric lesions on the palate in addition to the torso and lower extremities. Individual genetic factors and/or use of valproic acid in combination with lamotrigine may have facilitated the development of purpura.

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