INTERNAL MEDICINE

□ CASE REPORT □

Autoimmune Limbic Encephalitis and Syndrome of Inappropriate Antidiuretic Hormone Secretion Associated with Lamotrigine-induced Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) Syndrome

Lale Ozisik[1], Mine Durusu Tanriover[1] and Esen Saka[2]

Abstract

Drug rash with eosinophilia and systemic symptoms (DRESS) is a severe drug hypersensitivity reaction characterized by rash, fever and multi-organ failure. Limbic encephalitis (LE) is a rare disorder characterized by cognitive dysfunction with memory disturbance, seizures and psychiatric symptoms. We herein present an unusual case of DRESS syndrome due to lamotrigine with reactivation of Epstein-Barr virus, which developed autoimmune LE and syndrome of inappropriate antidiuretic hormone secretion. Discontinuation of lamotrigine, administration of methylprednisolone and intravenous immunoglobulin led to improvement. The LE in this case might have been caused by an autoimmune inflammatory mechanism associated with DRESS syndrome.

Key words: DRESS syndrome, autoimmune limbic encephalitis, syndrome of inappropriate antidiuretic hormone secretion, lamotrigine, DIHS

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Introduction

Drug rash with eosinophilia and systemic symptoms (DRESS) is a severe drug hypersensitivity reaction manifesting with rash, fever and multi-organ failure. The liver, kidneys, heart and/or lungs are most often affected. There are multiple names given to this syndrome, such as drug hypersensitivity, drug-induced delayed multi-organ hypersensitivity syndrome and drug-induced hypersensitivity syndrome (DIHS) (1). Cutaneous drug eruption, hematologic abnormalities including eosinophilia or the presence of atypical lymphocytes, and systemic involvement including adenopathies, hepatitis, interstitial nephritis, pneumonitis or carditis are the proposed criteria for the diagnosis of DRESS syndrome (2). In 2006, a Japanese consensus group established a set of criteria for the diagnosis of DRESS and called it DIHS; they included human herpesvirus 6 (HHV-6) reactivation in these diagnostic criteria (3).

The most common causative drugs of DRESS syndrome are antiepileptics and antimicrobials (1). Late onset, namely, two to six weeks after the initiation of drug therapy, and a prolonged course with flare-ups and relapses after withdrawal of the causative drug are typically observed. Recent studies demonstrated that HHV-6 and other herpesviruses, such as cytomegalovirus, Epstein-Barr virus (EBV) and human herpesvirus 7 (HHV-7), can be reactivated during the course of this syndrome (4).

The classical syndrome of LE includes the rapid development of irritability, depression, sleep disturbances, seizures, hallucinations and short-term memory loss. limbic encephalitis (LE) is now known to be a relatively common autoimmune disorder (5).

We present a case of DRESS syndrome with reactivation of EBV, which developed autoimmune LE and syndrome of inappropriate antidiuretic hormone secretion (SIADH) associated with lamotrigine.

[1]Department of Internal Medicine, Hacettepe University Faculty of Medicine, Turkey and [2]Department of Neurology, Hacettepe University Faculty of Medicine, Turkey
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Correspondence to Dr. Lale Ozisik, laleoz@gmail.com

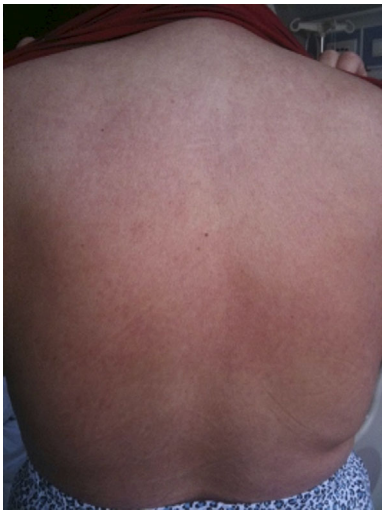

Figure 1. **Erythematous skin rash on the back.**

Case Report

A 37-year-old woman was admitted to our hospital with tremor, fever and skin eruptions. The rash had developed initially on her face and upper extremities, followed by the involvement of her trunk and lower extremities (Fig. 1). She had periorbital and facial edema. She also had dyspnea, which was progressive without cough.

In terms of her medical history, she had been diagnosed with bipolar affective disorder six years prior to presentation and her prior medication included valproic acid, lithium and quetiapine. Five weeks previously, lamotrigine treatment had been initiated and valproic acid had been tapered with the intention to stop its administration.

On a physical examination, she had diffuse pruritic maculopapular and erythematous rash with edema of the face and neck. Her pharyngeal reflex was hypoactive. She had postural and kinetic tremor. She also had rigidity, bradykinesia and hepatomegaly.

In terms of her laboratory findings, there were leukocytosis (19.3×10^3/μL) with eosinophilia (1.6×10^3/μL) and atypical lymphocytosis (7% of the peripheral blood elements). Other important laboratory findings were as follows: alanine aminotransferase: 172 U/L (<31), aspartate aminotransferase: 212 U/L (<33), alkaline phosphatase: 81 U/L (<390), gamma-glutamyl transferase: 184 U/L (<33), blood urea nitrogen: 10 mg/dL (6-29), creatinine: 0.7 mg/dL (0.5-0.9), sodium: 141 mEq/L (136-146), potassium: 3.8 mEq/L (3.5-5.1), calcium: 8.7 mg/dL (8.6-9.9) and phosphorus: 3 mg/dL (2.7-4.5).

Serological studies revealed that EBV virus capsid antigen (VCA) IgM was 4.1 (0-1) RU/mL, VCA IgG was 93 (0-20) RU/mL, early antigen D IgG was 72.4 (0-20) RU/mL and EBV nuclear antigen IgG was 168 (0-20) RU/mL. Two weeks later, VCA IgM became negative and VCA IgG was found to be 97 RU/mL, while EA IgG and EBNA IgG were still high, suggesting reactivation. Cytomegalovirus (CMV) IgM was negative and CMV IgG levels were 19 AU/mL (0.0-6.0) and 21 AU/mL in paired specimens obtained two weeks apart. In addition, CMV viral load was <150 copies/mL. Both IgM and IgG of HHV-6 were negative. We were not able to test for HHV-7, but other herpesvirus acute infections or reactivations were ruled out. The findings of histological examination of the patient's skin biopsy were compatible with drug eruption. Her bone marrow biopsy and aspirate revealed a normocellular bone marrow with an increase in megakaryocytes.

The patient was put on methylprednisolone (80 mg/day) treatment with the diagnosis of DRESS syndrome, lorazepam was initiated and lamotrigine was stopped. On the third day, the patient deteriorated progressively. She was disorientated and began to have difficulty walking and sitting in bed. She developed intention and resting tremors. She also had a mask face and rigidity. In addition, her pharyngeal reflex was diminished. The opening pressure of lumbar puncture was normal. Cerebrospinal fluid (CSF) protein was 20.7 mg/dL (15-45 mg/dL) and CSF glucose was 80 mg/dL, with a simultaneous serum glucose level of 109 mg/dL. No pleocytosis was evident. There were no oligoclonal bands and no viral DNA was identified by polymerase chain reaction (PCR) analysis in a CSF specimen. Serologic tests for antibodies specific for herpesviruses were all negative in the CSF. Magnetic resonance (MR) and diffusion MR imaging of the brain showed diffuse symmetrical high T2A intensity of bilateral hippocampus and amygdala (Fig. 2). In perfusion MR imaging, there was also decreased perfusion at these locations. Heart rate variability analysis demonstrated impairment in both sympathetic and parasympathetic systems. Electroencephalography showed diffuse, mild slow activity with no active epileptiform abnormality. Serum sodium declined progressively to a titer of 124 mEq/L, with normal renal and adrenocortical functions. The increased urine osmolality and decreased serum osmolality were suggestive of SIADH.

These clinical and radiological findings led us to a diagnosis of immune-mediated LE. Discontinuation of the drug and the administration of methylprednisolone led to an improvement; however, tapering of the methylprednisolone and the administration of lorazepam thereafter triggered clinical deterioration. We then initiated intravenous immunoglobulin (IVIG), tapered the lorazepam and thereafter stopped it.

Infection and malignancy were ruled out by various investigations of the possible cause of the LE. Tests for all antibodies against intracellular and cell-surface antigens, including N-methyl-D-aspartate receptor (NMDAR) antibodies, contactin-associated protein-like 2 (anti-Caspr2) antibody, leucine-rich glioma inactivated 1 (anti-LGI1) antibody, γ-aminobutyric acid-B receptor (GABA B ar B1/B2) antibodies, anti-glutamate receptor 1 (AMPA subtype) antibody and anti-glutamate receptor 2 (AMPA subtype), were found to be negative. With the treatment, the patient's facial edema, tremor and rigidity resolved, and her skin lesions and liver function improved. With water restriction, her sodium levels

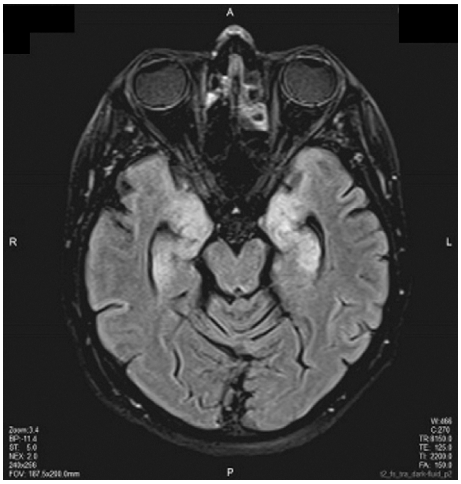

Figure 2. Axial fluid-attenuated inversion recovery (FLAIR) magnetic resonance image illustrating increased signals in bilateral hippocampus and amygdala.

were also normalized. The methylprednisolone was gradually tapered and the patient became able to sit in bed. After 30 days, her neurological status was completely improved and she was able to walk alone and had no tremor or rigidity. She was discharged with a dose-tapering plan for methylprednisolone and scheduled admission to our outpatient clinic.

Discussion

Although different mechanisms have been implicated, the pathophysiology of DRESS syndrome has not been fully understood. There is no consensus on the diagnostic criteria of this syndrome. According to a Japanese group, HHV-6 reactivation is a diagnostic criterion; however, EBV has also been found to be reactivated in the course of the syndrome (4, 6). It has been shown that the culprit drugs triggered the production of EBV in the patients' EBV-transformed B lymphocytes in an *in vitro* model based on immortalized B lymphocytes derived from DRESS patients. An increase of EBV production was observed not only with the culprit drugs, but also with other major DRESS inducers. However, these drugs did not induce EBV production in EBV-transformed B lymphocytes from healthy individuals (7).

In a study assessing patients with DRESS syndrome with herpesvirus reactivation, circulating CD8+ T lymphocytes were activated. Cutaneous homing markers were increased, and large amounts of tumor necrosis factor-alpha and interferon-gamma were secreted. Thus, cutaneous and visceral symptoms of DRESS are mediated by activated CD8+ T lymphocytes, which are directed against herpesviruses such as EBV (8). It has also been shown that EBV acts like an immunomodulator by encoding a protein resembling IL 10. Response to the virus might be an effect rather than a cause in patients with common autoimmune disease and cancer. Subsequent study of EBV suggested that herpesviruses can trigger the expression of superantigens that activate T-lymphocyte subsets, resulting in increased allergic cytokine expression and inflammation (9). Nevertheless, it is still not clear whether the reactivation of herpesviruses is part of the syndrome or is a complication, resulting in disease relapse (10).

Lamotrigine is an antiepileptic drug that is reported to induce DRESS syndrome (1). It is reported that the coadministration of valproic acid with lamotrigine is a risk factor for the development of rash (11). Our patient stayed on both lamotrigine and valproic acid treatment for a few days, which may have led to the development of DRESS syndrome. In the literature, there is only one reported case of lamotrigine-associated DRESS syndrome with the reactivation of herpesviruses (12).

LE refers to an inflammatory process involving the hippocampus, amygdala and, less frequently, frontobasal and insular regions (5). It can be infectious or autoimmune. MRI fluid-attenuated inversion recovery or T2 sequence showing a hyperintense signal in the medial aspect of the temporal lobes is a finding of LE. Our patient's MR abnormalities were indicative of LE. Autoimmune LE can be both paraneoplastic and non-paraneoplastic. In the absence of onconeural antibodies against intracellular antigens, it is more likely to be the latter. Neuronal antibodies against cell-surface antigens, such as voltage-gated potassium channel and NMDAR, have been found in a number of patients with LE, but are not necessarily associated with cancer. There is a group of patients who develop classical LE but are negative for all known antibodies, suggesting seronegative autoimmune LE (5). In our patient, screening for known antibodies was also negative, suggesting this condition. LE caused by EBV was shown in patients who underwent allogeneic stem cell transplantation (13). However, in our patient, PCR analysis of the CSF was negative for EBV and all other viruses. Many of the aspects of the mechanisms of DRESS syndrome and LE suggest similarities between them. DRESS syndrome is also mediated by cytotoxic T cells, which are directed against herpesviruses (8); hence, the LE in our patient might have been caused by an autoimmune inflammatory mechanism associated with DRESS syndrome and EBV reactivation.

In the literature, there are three reported cases of DRESS syndrome-associated LE. HHV-6 reactivation was seen in all of them, but there were no cases with EBV reactivation. In all of these three cases, the offending drug was phenobarbital. Only in one of them was PCR of the CSF positive for HHV-6 (14). In the other cases, it was negative, suggesting an autoimmune mechanism behind the LE (15, 16). In one of these case reports, LE-associated SIADH in a patient with DRESS syndrome was diagnosed, like in our patient. This patient developed HHV-6 reactivation, but PCR of the CSF was negative for it (16). Our patient's MR imaging did not suggest pituitary involvement. EBV reactivation in the setting of DRESS syndrome may be responsible for SIADH, like in the other case with HHV-6 (16).

This is the first reported case of lamotrigine-induced DRESS syndrome with EBV reactivation, which revealed LE and SIADH. Although the tests with antibodies were negative, our patient responded well to the treatment with IVIG and methylprednisolone, which suggested seronegative autoimmune LE.

We concluded that the LE in our patient might have been caused by an autoimmune inflammatory mechanism associated with DRESS syndrome. It is not clear whether the reactivation of EBV is a cause or complication of the syndrome. The choice of therapy after discontinuation of the culprit drug must be made carefully, in order not to cause any other autoimmune sequelae.

The authors state that they have no Conflict of Interest (COI).

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