Case Report

Carbamazepine-associated Drug Reaction with Eosinophilia and Systemic Symptoms Syndrome

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INTRODUCTION

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a severe type IV hypersensitivity reaction and usually begins after a few weeks of latency period. This reaction is characterized by fever, rash, lymphadenopathy, and systemic inflammatory involvement. The pathogenesis is not fully understood and may be multifactorial, involving immunological mechanisms, particularly drug detoxification pathways.[1,2] The association of slow acetylation with an increased risk of DRESS syndrome highlights the importance of drug metabolism in its causation. It has also been suggested that concomitant human herpes virus 6 (HHV-6) infection increases the risk to develop DRESS syndrome.[3] The unpredictability, potential severity, and no consensus in management protocol makes it a major concerned entity in clinical practice.

CASE REPORT

A 13-year-old boy presented in the neurology outpatient department with symptoms suggestive of right-sided partial motor seizures with secondary generalization due to left frontal focal cortical dysplasia. He was started on carbamazepine 100 mg once a day, and his dose was increased in increments of 100 mg every fourth day. His seizures were controlled on 800 mg of carbamazepine, and he continued with the treatment. On the 25th day of his treatment, he developed maculopapular rash all over his body, particularly severe on his face, neck, trunk, and legs [Figure 1A and B]. He was febrile with a temperature of 38°C. His examination revealed tender lymphadenopathy of axillary and cervical region with hepatomegaly. Rest of the systemic examination was normal. His investigations revealed hemoglobin of...
12.3 g/dL, total leukocyte count of 16,300 µL, differential leukocyte count—polymorphs: 54%, lymphocyte: 28%, eosinophil: 16%, monocyte: 2%, and alanine aminotransferase (ALT) and aspartate aminotransferase were more than four times the upper limit of normal. His blood and urine cultures were sterile. Chest X-ray was normal. Tests for hepatitis A, B, and C were negative. HIV serology was nonreactive. He was diagnosed as a case of DRESS syndrome, and his carbamazepine was stopped, injection methylprednisolone 1 g intravenous, once a day for 5 days was started along with antihistaminics. He was shifted to levetiracetam from carbamazepine for seizure control. The patient improved over the next 2 weeks with complete resolution of maculopapular rash [Figure 1C], and lymphadenopathy too subsided. Transaminitis resolution took another week, and he was discharged from the hospital in a hemodynamically stable state.

**DISCUSSION**

DRESS syndrome was first described by Bocquet et al. It is a severe type IV hypersensitivity reaction, and it usually begins a few weeks after the exposure to offending drug. Pathomechanism of DRESS syndrome is complex and is still not well understood. Plausible mechanisms could be the complex interplay of immune-mediated hypersensitivity as a result of interaction between the metabolites of drugs in a genetically susceptible individual.

In a genetically susceptible individual, drug or its metabolite gets accumulated due to altered activity of metabolizing enzymes. These metabolites then evoke drug-specific T lymphocytic reaction, leading to clinical presentation of DRESS syndrome. On the contrary, antidrug immune response or accumulated metabolites can incite “viral reactivation,” which can induce profound antiviral response leading to DRESS syndrome.

Most commonly implicated drugs in DRESS syndrome are aromatic anticonvulsants (phenytoin, phenobarbitone, and carbamazepine) and sulfa drugs (sulfonamides, sulfasalazine, and dapsone). Like all hypersensitivity reactions, DRESS syndrome too presents with rash, swelling, and eosinophilia, but the hallmark of the reaction is systemic inflammatory involvement of liver, heart, kidneys, and other organ systems.

Most commonly used diagnostic guidelines were developed by a Japanese working group in 2007. The guidelines require the following:

1. Development of maculopapular rash after 3 weeks of initiation of offending drug
2. Prolonged clinical symptoms 2 weeks after discontinuation of the offending drug
3. Fever >38°C
4. Hepatic involvement (including ALT >100 U/L)
5. Leukocytosis >11 × 10^9/L or atypical lymphocytosis or eosinophil count >1.5 × 10^9/L
6. Lymphadenopathy
7. HHV-6 reactivation

Our patient met the first six criteria, and his HHV-6 DNA assay was not done.

The mainstay of treatment in such cases is prompt withdrawal of offending drug and introduction of steroids. Recently, a consensus outline for the management of such patients was given by Descamps et al., they recommended systemic corticosteroids (equivalent dose of 1 mg/kg/day of prednisone) in patients with transaminase levels more than five times the upper limit of normal, pneumonia, renal impairment,
cardiac involvement, or hemophagocytosis. In cases of life-threatening features, including respiratory or renal failure, they have recommended intravenous immunoglobulin in a dose of 2g/kg over 5 days. The group has also proposed the use of steroids in combination with ganciclovir in patients with signs of severity and confirmation of a major viral reactivation of HHV-6.

Our patient met the diagnostic criteria and was treated with intravenous steroids in recommended doses with an excellent outcome.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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