Drug Reaction with Eosinophilia and Systemic Symptoms Syndrome: Quick Defervescence with Early Steroid Therapy

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Abstract

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome or drug-induced hypersensitivity syndrome or anticonvulsant hypersensitivity syndrome is a delayed hypersensitivity drug rash that occurs 2–6 weeks after starting anticonvulsants, sulphonamides, or antibiotics. It is characterized by a triad of fever, rash, and systemic manifestations with an overall mortality of 10%. We reported a 1½-year-old girl who was a known case of structural West syndrome and was on phenobarbitone, valproate, and levetiracetam. She presented with fever, rash, liver dysfunction, and eosinophilia. Diagnosis of DRESS was considered and was treated with IV methylprednisolone following which she showed rapid defervescence, healing of rash, and improvement in liver dysfunction within the next 4 days. Rapid response to specific therapy made us report this case.

Keywords: Anticonvulsant, Eosinophilia, Liver dysfunction, Steroids.

Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a rare, idiosyncratic, delayed hypersensitivity drug reaction that occurs classically 2–6 weeks after starting anticonvulsants (carbamazepine, phenytoin, phenobarbitone, oxcarbazepine, lamotrigine), other drugs (sulphonamides, minocycline, allopurinol, dapsone, sulfasalazine, etc.), and antibiotics and it is potentially life-threatening.1–3 The estimated incidence of DRESS syndrome ranges from 1 in 1,000 to 1 in 10,000 drug exposure (1 in 1,500 new users of phenytoin and carbamazepine) and mortality as high as 10%.4 The treatment includes withdrawal of offending medication, supportive care, and systemic steroids.4

The reason for reporting this case is to describe a child with characteristic features of DRESS syndrome due to antiepileptic drugs and who responded quickly to pulse methylprednisolone. There are only limited reports in the literature where children with DRESS syndrome were treated with pulse methylprednisolone. The clinicians should be aware of this complication as early recognition and prompt management may be life-saving.

Case Description

We report a 1½-year-old girl, known case of West syndrome receiving phenobarbitone (5 mg/kg/day), valproate (40 mg/kg/day), and levetiracetam (20 mg/kg/day) for the last 6 months. She developed sudden onset of febrile illness with generalized erythematous, maculopapular, pruritic rash involving face, trunk, and limbs (Figs 1A and B). In 3–4 days, the rash became confluent. She also had generalized edema which was more pronounced over face and trunk (Fig. 1A) and dorsum of hands and feet.

Laboratory investigations revealed eosinophilia (1,690/mm³), transaminitis [AST 197 U/L (normal: 13–35 U/L) and ALT 192 U/L (normal: 5–45 U/L)], coagulopathy (INR 2.3), normal renal functions, and elevated CRP [19.5 mg/dL (normal: <0.5 mg/dL)]. Serology for EBV, Mycoplasma, CMV, HAV, HBV, HCV, and Chlamydia were negative and blood culture was sterile. The RegiSCAR score was 7. The treatment included discontinuation of phenobarbitone and valproate, continuation of levetiracetam, and addition of clobazam.

In view of systemic involvement, she received intravenous methylprednisolone (30 mg/kg/day) for 3 days followed by oral prednisolone (2 mg/kg/day). There was rapid defervescence, healing of rash (Fig. 1C), and improvement in liver dysfunction within next 5 days.

Discussion

The common anticonvulsant drugs leading to DRESS syndrome are carbamazepine, phenytoin, phenobarbitone, oxcarbazepine,
Drug Reaction with Eosinophilia and Systemic Symptoms Syndrome

It presents as a spectrum from mild rash with hematological manifestation which response to the withdrawal of offending drug to severe multiorgan involvement requiring immunosuppression. It is characterized by a triad of fever, rash, and hepatitis. The rash is initially located over the face, upper trunk, and arms in form of diffuse exanthem of morbilliform pruritic papules to plaques. Exfoliation is uncommon and so is the mucous membrane involvement. Eosinophilia (≥500/μL) and atypical lymphocytosis are common features but not always present. There may be facial edema, cervical lymphadenopathy, pharyngitis, and malaise. Multisystemic involvement in form of hepatitis (90%) (ranging from a mild elevation of liver transaminase values to frank hepatic failure), interstitial nephritis (9%), pneumonia (5%), myocarditis, shock, and encephalitis can occur in severe disease.

Diagnosis of DRESS syndrome is difficult to establish, and it requires a high level of suspicion as well as ruling out other etiologies. These include infectious disease (e.g., viral exanthemas, staphylococcal and streptococcal toxic shock syndromes, meningococemia), non-infectious drug eruptions (e.g., Stevens–Johnson syndrome, toxic epidermal necrolysis), autoimmune disease (e.g., Kawasaki disease, hypereosinophilic syndrome), and neoplastic diseases (e.g., leukemia cutis, mycosis fungoides). Depending on the specific organs involved, the differential diagnosis also includes viral hepatitis (liver), glomerulonephritis, vasculitides, pre- and post-rerenal causes of acute kidney injury (kidney), Kawasaki disease and eosinophilic myocarditis (heart), parasitic infection (gastrointestinal tract), and bacterial, viral, and fungal pathogens (lungs). There are no available pathognomonic signs or diagnostic tests. The diagnosis is clinical and established by taking into account drug exposure in the appropriate clinical setting and latency between drug exposure and symptom onset. Re-challenging with the causative drug has been the gold standard to diagnose drug eruptions but should not be used in suspected DRESS cases as it may be life-threatening. The most commonly used diagnostic criteria included a scoring system proposed by the RegiSCAR group. This scoring system comprises the major features of DRESS syndrome, giving each item a score of minus one point, zero points, one point, or two points. The diagnosis of DRESS syndrome is then made based on the total score: <2 points: no case; 2–3 points: possible case; 4–5 points: probable case; ≥5 points: definite case. In the index case, she had fever, lymphadenopathy, eosinophilia, skin rash (>50% of BSA), and organ dysfunction (liver dysfunction). So, the RegiSCAR score was 7 making her a definite case of DRESS syndrome.

Treatment of DRESS syndrome includes the immediate withdrawal of inciting drugs. Cross-sensitivity of barbiturates and carbamazepine with phenytoin has been observed. In such a setting, the drugs that can be safely used to control seizures are levetiracetam, valproate, and gabapentin. The systemic corticosteroids are the mainstay of treatment for a patient with DRESS syndrome. IVIG is another treatment option used in various case reports yielding conflicting results. In severe and corticosteroid-resistant cases, more potent immunosuppressants including cyclosporine, azathioprine, rituximab, infliximab, and mycophenolate have been used, sometimes alongside adjunctive treatment with IVIG and plasmapheresis. N-Acetyl cysteine (NAC), which acts as a detoxifying drug, can also be used in DRESS syndrome. In addition to definite treatment, supportive care is also important to support involved organ dysfunction.

**CONCLUSION**

Clinicians should be aware of this potentially fatal cutaneous drug reaction and common medications implicated in the causation of DRESS syndrome. The prompt withdrawal of the offending drugs and early introduction of systemic steroids in severe cases may lead to a better outcome.

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