Case 47. A 2-Month-Old Infant with Fever, Progressive Skin Rash and Eosinophilia: Drug-Induced Fever and Skin Rash in Children

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Keywords

Drug reaction with eosinophilia and systemic symptoms (DRESS) · Drug-induced hypersensitivity syndrome (DIHS) · Adverse drug eruption · Skin rash · Antibiotics · Allergy

Key Points

- Drug reaction with eosinophilia and systemic symptoms (DRESS) is a syndrome characterized clinically as an extensive infiltrative maculopapular exanthem accompanied by fever, lymphadenopathy, internal organ involvement, and hematological abnormalities.
- Generalized, infiltrated papuloplaques with purpuric change, facial edema, and desquamation are suggestive dermatological features.
- Manifestations of DRESS range from mild disease to severe internal organ involvement with potential life-threatening consequences.
- Early recognition and withdrawal of the offending drug are key to managing for patients with this severe cutaneous adverse drug reaction.
- Systemic corticosteroid remains the first-line treatment for DRESS; cyclosporine or tofacitinib have been used for recalcitrant cases.

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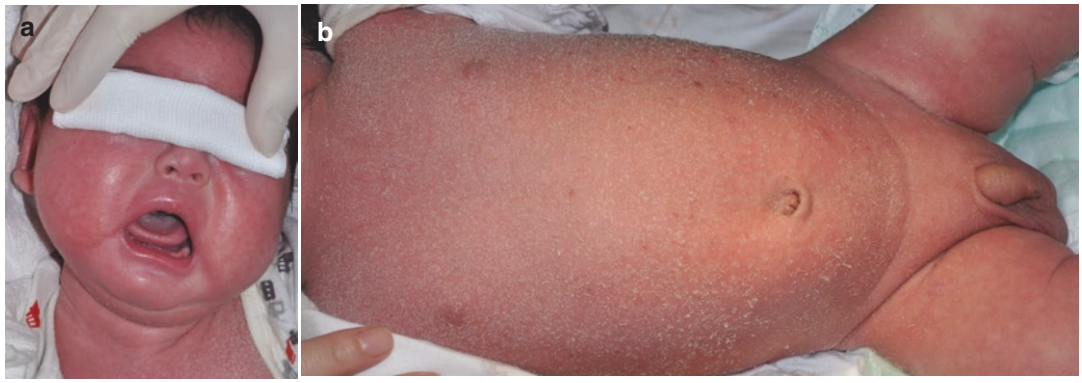

Fig. 1 Clinical picture of the 2-month-old boy with DRESS. Skin examination showed facial swelling with generalized infiltrative erythema on the face (**a**), and trunk, and lower extremities. Scaling on the erythrodermic skin (**b**) was also noticed days later

Case Report

A 2-month-old male infant was admitted to the neonatal unit due to progressive skin rash and fever with decreased appetite and activity for 3 days. Skin examination showed generalized, infiltrative erythematous maculopapular rash with areas of confluent erythema. Facial swelling (Fig. 1a) and bilateral cervical lymphadenopathy were also noted. Laboratory data demonstrated leukocytosis and eosinophilia (white blood cell count 25,100/μL with 0.5% bands, 51.5% segmented cells, 27.5% lymphocytes, 5.5% monocytes, 6% eosinophils, and 9% atypical lymphocytes), platelet count 307,000/μL, and hemoglobin 10.5 g/dL. Blood biochemistry data showed elevated liver enzymes (aspartate transaminase 395 U/L, alanine transaminase 677 U/L), gamma-glutamyl transferase 600 U/L, alkaline phosphatase 233 U/L, serum bilirubin direct/total 0.2/0.3 mg/dL, blood urea nitrogen 10.1 mg/dL, serum creatinine 0.24 mg/dL, and C-reactive protein 25.28 mg/L. Based on the clinical impression of drug reaction with eosinophilia and systemic symptoms (DRESS), skin biopsy was performed on an infiltrated plaque lesion of the abdomen. The histopathology revealed basket weave hyperkeratosis, scattered dyskeratotic cells in the epidermis with necrotic keratinocytes of basal layer, mild vacuolar interface change, and perivascular lymphocytic infiltrates. The pathological finding was consistent with DRESS. Further serological tests for hepatitis B virus, hepatitis C virus, Epstein-Barr virus (EBV), cytomegalovirus (CMV), *Mycoplasma pneumonia*, anti-nuclear antibody, and blood culture were all negative. Based on the Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) criteria, a definite case of DRESS was diagnosed (Kardaun et al. 2013).

Under the diagnosis of DRESS syndrome, systemic corticosteroid with intravenous methylprednisolone (1 mg/kg/day) was administered for 2 weeks. However, due to the progression of skin lesions with persistent fever, eosinophilia, and elevated liver enzymes, treatment with cyclosporine (1 mg/kg/day) was added. The skin eruption, hematological abnormalities and elevated hepatic enzymes gradually improved after 2 months of treatment. Scaling on the erythrodermic skin (Fig. 1b) was also noticed days later.

According to the boy's drug history, he was given amoxicillin for about 10 days for respiratory tract infection before the onset of skin eruption. Further lymphocyte activation test confirmed the culprit drug as amoxicillin.

Discussion

DRESS is potentially life-threatening severe cutaneous adverse drug reactions (SCARs) that can occur in both adults and children. DRESS, also known as drug induced hypersensitivity syndrome (DIHS), presents clinically as an extensive

maculopapular exanthem accompanied by fever, lymphadenopathy, internal organ involvement (such as hepatitis and nephritis), and hematological abnormalities, including eosinophilia and elevated atypical lymphocytes. Drugs such as aromatic antiepileptics and antibiotics have been most commonly associated with DRESS in children.

In most patients, the reaction begins 2–6 weeks after the initiation of the offending medication (Afiouni et al. 2021), with an average latency of 18.9 days in one review of pediatric DRESS cases. This latency between drug exposure and onset of symptoms in DRESS is considerably longer than in most other drug eruptions. However, asymptomatic changes in lymphocyte blood count or liver function tests may begin earlier.

The skin eruption usually starts as a morbilliform eruption that progresses to become diffuse, confluent, infiltrated papuloplaques. The eruption becomes suggestive of DRESS when it involves more than 50% of the body surface area and includes two or more of the followings: edema (especially facial edema), infiltrated skin lesions, scaling/desquamation, or purpura. The face, upper part of the trunk, and extremities are often involved initially. DRESS in children most often presents as diffuse maculopapular exanthem, with facial edema and oral mucosal involvement in 30% and 20%, respectively. Systemic organ involvement is common, especially involving the liver, kidneys, and lungs. Other severe cutaneous drug eruptions, viral or bacterial infections, Kawasaki disease, hypereosinophilic syndrome, lymphoma, febrile mucocutaneous syndrome, and autoimmune connective tissue diseases may also present with clinical symptoms that mimic DRESS. Exclusion of these other etiologies can help validate a diagnosis of DRESS.

A drug-specific immune response contributes to the pathogenesis of DRESS. During the acute phase of disease, there is an expansion of activated T lymphocytes in the blood, including both CD8 and CD4 cells, and an expansion of regulatory T cells. The frequent peripheral blood eosinophil activation and high serum levels of interleukin-4, interleukin-5, interleukin-13, and thymus and activation-regulated chemokine/chemokine ligand 17 in DRESS patients indicate that the Th2-type immune response also plays a major role. Reactivation of several viruses of the herpes group (human herpesvirus [HHV]-6, HHV-7, EBV, and CMV) is frequent in DRESS and can contribute to clinical symptoms or complications.

Identification and prompt withdrawal of the offending drug is crucial for patients with DRESS. New medications should be introduced carefully during the course of DRESS and in patients in whom DRESS is suspected. Of note, selection of structurally different alternative drugs is important to prevent recurrence. Systemic corticosteroids are usually the first-line treatment for DRESS with extensive rash and severe organ involvement in both adults and children. Though the efficacy and side effect of corticosteroids have not been evaluated in randomized trials to our knowledge, there is general consensus among experts on the use of systemic corticosteroids for the treatment of DRESS with severe organ involvement. There have been cases reports of rapid resolution of DRESS using oral cyclosporine, which can be considered for patients who do not respond well to systemic corticosteroids or when corticosteroids are contraindicated (Su et al 2021). A recent study reported satisfactory control of a recalcitrant and refractory DRESS after 2 weeks of tofacitinib, an inhibitor of the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway. Finally, because viral reactivation can cause severe complications such as encephalitis, hemophagocytosis, or severe erosive colitis, antiviral agents active against HHV-6 or CMV may be warranted.

Most patients with DRESS recover completely in weeks to months after drug withdrawal and appropriate treatment. The prognosis of DRESS in children tends to be better with lower mortality compared to adults. However, sequelae with autoimmune diseases have been reported in some patients months or years after the resolution of the drug reaction, including vitiligo, Graves' disease, type 1 diabetes mellitus, and autoimmune hemo-

lytic anemia. One systematic review of DRESS in pediatric patients found a death rate of 3%, with 8% reporting autoimmune sequelae. In the same review, almost 5% of the children with DRESS had a recurrent or relapsing course, which was associated with more comorbidities such as renal and pulmonary involvement. In this group of relapsing pediatric DRESS, initial presentation with erythroderma, facial edema, fever, lymphadenopathy, and prolonged leukocytosis were more frequently detected.

Further Reading

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