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CASE REPORT

Diagnosing drug reaction with eosinophilia and systemic symptoms in a medically complex young child

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Case Report

A 2-year-old girl, weighing 5 kg, with Wolf-Hirschhorn syndrome (WHS) was admitted to the Perth Children's Hospital in Western Australia following the initial onset of multiple seizures and coryza. Her remaining past medical and family history was unremarkable. She was commenced on multiple antiepileptics: levetiracetam on admission, then phenobarbitone on Day 3 and sodium valproate on Day 9 of her admission respectively.

She was subsequently diagnosed with human metapneumovirus pneumonitis, Haemophilus influenzae pneumonia and a methicillin-resistant Staphylococcus aureus infection of her percutaneous endoscopic gastrostomy site. She was commenced on antibiotic therapy: amoxicillin from Days 6 to 8, amoxicillin/clavulanic acid for Days 8–9 then co-trimoxazole on Days 9–11 of her admission.

On Day 10 of admission, the patient developed a widespread erythematous maculopapular rash. The rash initially had a mottled appearance which changed to an erythematous, eczematous rash to her limbs that was warm to touch and a maculopapular rash to her trunk. The rash was associated with a fever of 37.8°C. Considering a possible antibiotic allergy, co-trimoxazole was ceased as it was the last medication that was commenced. On Day 13 of admission, the patient developed increased oxygen requirements, a peak temperature of 40.2°C was recorded and she was noted to have generalised facial oedema. She was transferred to the Paediatric Intensive Care Unit for overnight observation with suspected sepsis before she was stepped down to the ward. During this episode, she received i.v. meropenem and i.v. vancomycin for 2 days (Days 13 and 14 of her admission).

The rash continued to worsen which prompted a review of the antibiotics and anti-epileptics that had been commenced since admission (see Fig. 1). Other associated significant clinical features included swelling of her face, hands and feet and a fever of 38.7°C on Day 15 and Day 16 of her admission. There was no evidence of mucosal or genital involvement.

On Day 15, she developed eosinophilia which peaked at 1.32×10^9/L and gradually resolved by Day 23. Laboratory investigations also revealed deranged liver function tests (alkaline phosphatase 93–103 U/L, gamma-glutamyl transferase 27–87 U/L and albumin 27–29 g/L) and raised inflammatory markers (peak levels – C-reactive protein 79 mg/L, platelets 1666 $\times 10^9$/L) which started on Day 13. Of note, hepatitis A, B and C serology, antinuclear antibody, mycoplasma pneumoniae and blood cultures were negative. Due to issues with blood sample collection, HHV 6 and *Chlamydia psittaci* serology were not processed.

Drug reaction with eosinophilia and systemic symptoms (DRESS) RegiSCAR scoring was performed – yielding a score of 4 (fever ≥38.5°C, eosinophilia, skin rash suggesting DRESS and skin rash extent >50% body surface area, liver involvement and evaluation of other potential causes were negative) – consistent with a probable diagnosis of DRESS.[1]

Phenobarbitone was thought to be the most likely causative agent of DRESS in this patient due to the clinical correlation between commencement of this drug and the development of the rash and subsequent clinical deterioration (Fig. 2). Vancomycin was considered to be a potentiating agent as the rash and eosinophilia worsened after its introduction. Both drugs were ceased and as per the mainstay of treatment for DRESS, oral prednisolone (1 mg/kg/dose) was commenced on Day 16.[2] Clinically, her rash vastly improved after the introduction of prednisolone and topical corticosteroid creams and emollients. The patient was discharged when blood results trended towards normal and when there was clinical improvement of the rash.

She was advised to avoid phenobarbitone and vancomycin lifelong and to avoid amoxicillin, amoxicillin/clavulanic acid, trimethoprim and sulfonamides until further drug patch testing. Follow-up patch testing could not be performed as the patient unfortunately passed away 4 months after due to unrelated circumstances.

Key Points

1 Early accurate diagnosis of drug reaction with eosinophilia and systemic symptoms (DRESS) can be challenging in patients with a rash on multiple new medications with an associated viral infection.
2 Our case highlights that paediatricians should be aware of the clinical presentation of DRESS syndrome, especially in medically complex children receiving new anti-epileptics or antibiotics.
3 The removal of the offending drug is paramount in DRESS and topical and/or oral corticosteroids can be used to hasten disease resolution.

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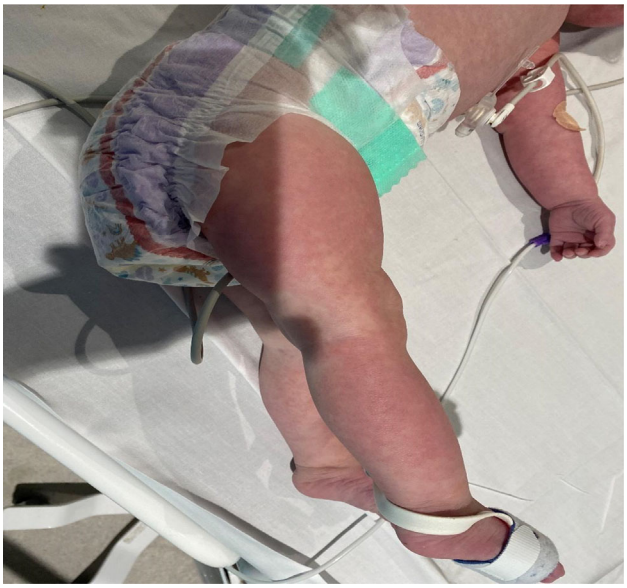

Fig. 1 Patient's skin rash on Day 14.

Discussion

DRESS is a rare, potentially life-threatening drug-induced hypersensitivity reaction. It is characterised by widespread cutaneous eruption, fever, haematologic abnormalities, lymphadenopathy and visceral organ involvement. Incidence is estimated to be between 1:1000–1:10 000 cases, with a reported mortality of 10% in adults.[1] Prompt recognition and management of DRESS are crucial in any age group because its clinical manifestations can be severe and potentially deadly.

This report uniquely describes a case of DRESS in a medically complex, very young child with WHS secondary to the introduction of phenobarbitone. WHS is a rare congenital disorder which is associated with craniofacial changes, cardiac defects, epilepsy, growth and developmental retardation. Associated immune defects have been described such as common variable immunodeficiency, IgA deficiency and impaired polysaccharide responses. This may pre-dispose to an increased risk of severe cutaneous adverse reactions.[2]

To our knowledge, this is the first Australian case described in this young age.[3] Diagnosis of DRESS can be challenging, especially in complex paediatric conditions. Furthermore, symptoms of DRESS can mimic other conditions such as infection, malignancy or autoimmune disease. Accurate diagnosis was even more challenging due to the difficulty in determining if the rash was caused by infection or treatment. Diagnosis is based on clinical criteria listed in the 2007 RegisCAR scoring guidelines, which include fever, lymphadenopathy, eosinophilia, lymphocytosis, rash, biopsy, organ involvement, clinical course and the exclusion of other causes.[1] Our patient's symptoms of cutaneous eruption, fever, eosinophilia and liver derangement were consistent with DRESS syndrome. The presence of eosinophilia helped to narrow the differential diagnoses. Facial oedema is also a less commonly known but recognised symptom of DRESS which further confirmed our accurate diagnosis in this case.[4] A skin biopsy was considered but decided against as this would have been an invasive procedure in a very unwell young child who already fulfilled clinical criteria for DRESS (according to 2007 RegisCAR scoring guidelines) with an excellent response to steroid therapy.

Human leukocyte antigens (HLA)-typing did not reveal alleles associated with relevant drug-induced hypersensitivity, such as HLA-A*32:01 which is associated with vancomycin-induced DRESS, or HLA-A*01:01 and HLA-B*13:01 which are associated with phenobarbitone hypersensitivity.[5,6] However, our patient did possess HLA-A*24:02 which is associated with lamotrigine and phenytoin-induced DRESS as well as Stevens-Johnson syndrome induced by the aromatic anti-epileptic drug group, suggesting that this allele may play a role in phenobarbitone-induced DRESS.[7,8]

In most cases of DRESS, the reaction begins 2–8 weeks after initiation of the causative drug however, these reports are based on adults and data in early childhood are not present. In our patient's case, her rash began 7 days after commencement of the suspected culprit drug, phenobarbitone which is consistent with early-onset DRESS syndrome.[4]

Drugs most implicated are antiepileptics (50%), including phenobarbitone (11.5%). The second most common causative drugs are antibiotics (30.8%) – most commonly vancomycin and trimethoprim-sulfamethoxazole.[5] Phenobarbitone was likely the

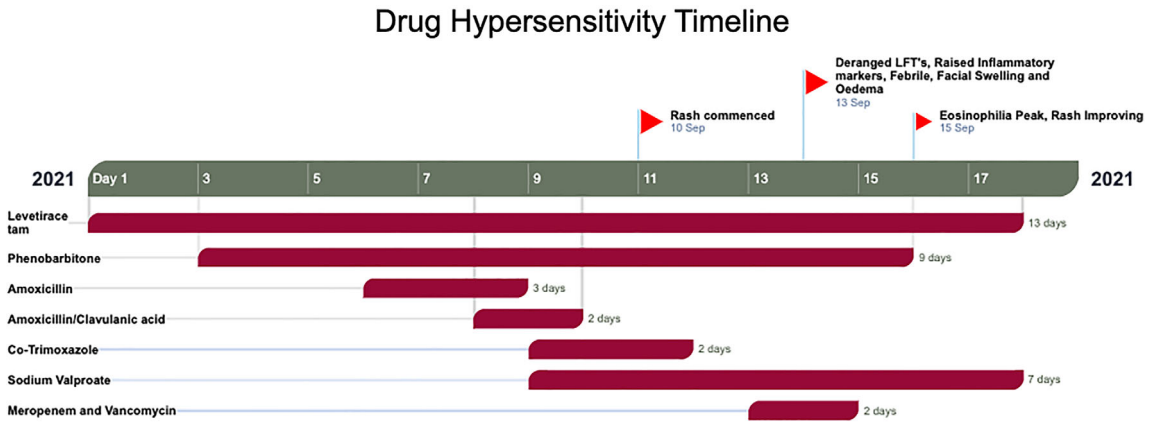

Fig. 2 Patient's drug hypersensitivity timeline.

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culprit agent in the case of our patient due to the clinical correlation between commencement of this drug and the development of the rash and subsequent clinical deterioration. The rash and biochemical markers were abnormal but worsened on introduction of vancomycin, excluding it as an initiator. However, vancomycin may have potentiated the reaction.

Identification and withdrawal of the causative drug with supportive treatment is the mainstay of treatment for patients with DRESS. Treatment with topical and/or systemic corticosteroids depending on DRESS severity can also hasten resolution of the rash and other symptoms.[4]

Accurate diagnosis of DRESS and careful consideration of differential diagnoses is important to ensure timely disease management and avoid inappropriate mislabelling of medication sensitivity which would limit future therapeutic options.

The legal guardian has consented to publish this case report.

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Let's fly by Ian Kim (aged 8) from "A Pop of Colour" art competition, Youth Arts, Children's Hospital at Westmead

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