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Case 2: Where did you get that DRESS?

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Case 2: Where did you get that DRESS?

A 14-year-old teenage girl with a known seizure disorder presented to the emergency department (ED) with fever, extensive maculopapular rash, facial edema and odynophagia. Twenty-four days earlier, she had been placed on phenytoin and cephalexin after cranial lesionectomy surgery for epilepsy. Other medications included therapy for the previous two years with oxcarbazepine and valproic acid. She had no known allergies.

Her symptoms had begun one week earlier with a mild morbilliform rash and fever. She was seen in the ED at that time, and both the phenytoin and cephalexin were discontinued. In the following days, her rash extended and became pruritic with associated facial swelling. Due to worsening of her symptoms and continuing fever, she returned to the ED.

On examination, she was alert and oriented, but appeared unwell with a fever of 39°C. There was significant angioedema of her face and ears (Figure 1), cervical lymphadenopathy, and an extensive rash (Figure 2) on her entire trunk, buttocks, extremities and face; her palms and soles were spared. A review of her systems was otherwise unremarkable; specifically, she experienced no joint pain or neurological symptoms, and no abdominal or respiratory complaints. She denied any allergies, sick contacts or recent travel, and her immunizations were up to date.

Investigations revealed an elevated C-reactive protein level (96 mg/L [normal 0 mg/L to 8 mg/L]), normal erythrocyte sedimentation rate and mild leukocytosis (12.7×10^9/L [normal 4×10^9/L to 10×10^9/L]), with elevated bands (2.29×10^9/L [normal 0.00×10^9/L to 0.01×10^9/L]) and eosinophilia (1.14×10^9/L [normal 0.02×10^9/L to 0.50×10^9/L]). Hemoglobin (137 g/L [normal 120 g/L to 153 g/L]) and platelets (166×10^9/L [normal 150×10^9/L to 400×10^9/L]) were normal. Liver enzymes were mildly elevated (alanine aminotransferase 64 U/L [normal 0 U/L to 40 U/L], aspartate aminotransferase 68 U/L [normal 0 U/L to 36 U/L], gamma-glutamyl transpeptidase 397 U/L [normal 0 U/L to 43 U/L]). The creatinine level and a urinalysis were normal. A throat swab culture for group A streptococcus and an antistreptolysin O titre were sent. Heterophile antibody, Epstein-Barr virus and cytomegalovirus titres, as well as blood and urine cultures were sent. A chest x-ray and electrocardiogram were unremarkable. A provisional diagnosis was made based on the findings described above.

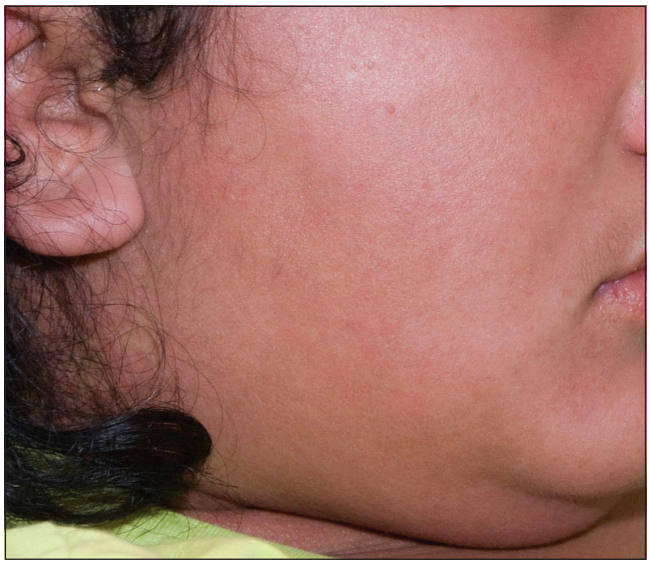

Figure 1) *Significant angioedema of the patient's face and ears in Case 2*

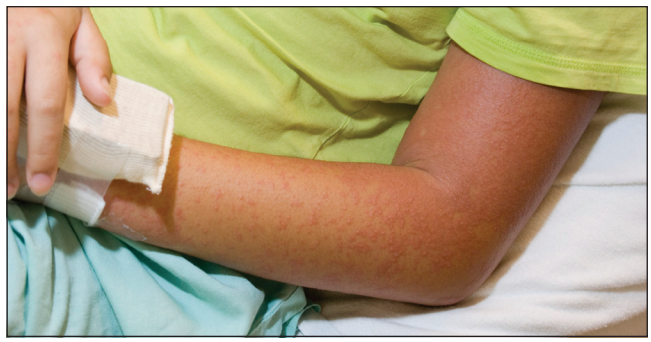

Figure 2) *An extensive rash on the patient's arm in Case 2*

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CASE 2 DIAGNOSIS: DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS

The patient was admitted to hospital with a diagnosis of drug reaction with eosinophilia and systemic symptoms (DRESS). She was treated with intravenous methylprednisolone (1 mg/kg/day) to control inflammation and oral hydroxyzine for pruritus. Liver enzymes rose to a maximum of 109 U/L for alanine aminotransferase (normal 0 U/L to 40 U/L), 72 U/L for aspartate aminotransferase (normal 0 U/L to 36 U/L) and 485 U/L for gamma-glutamyl transpeptidase (normal 0 U/L to 43 U/L), but had begun to decline by discharge. Baseline thyroid function tests (thyroid-stimulating hormone, free thyroxine and triiodothyronine) were normal. During her five-day hospital admission, the rash, angioedema and lymphadenopathy all improved. She defervesced and was switched to oral steroids. All cultures and the cytomegalovirus, Epstein-Barr virus, group A streptococcus and anti-streptolysin O titres were normal, but her test for human herpes virus (HHV)-7 DNA by polymerase chain reaction was positive. She was switched from oxcarbazepine to levetiracetam (Keppra; UCB Canada Inc) despite tolerating the former for two years, due to concern about cross-sensitivity among aromatic anticonvulsant drugs.

DRESS secondary to antiepileptics is rare, occurring in one per 1000 to one per 10,000 new exposures to causative agents, and approximately one per 1,000,000 persons/year. Drugs commonly associated with DRESS are allopurinol, carbamazepine, phenytoin, phenobarbital, sulphasalazine, lamotrigine and azathioprine. DRESS is a potentially fatal adverse reaction that typically occurs two to eight weeks following initiation of drug therapy, and is distinguished by a triad of fever, morbilliform rash and systemic organ involvement; usually, hepatitis occurs, although renal, neurological, cardiac and lung involvement are possible. Rarely, the rash is exfoliative, which is similar to Stevens-Johnson syndrome. Other features include lymphadenopathy (75%), arthralgias, facial edema, malaise and pharyngitis. Laboratory features include evidence of hepatitis (51%), interstitial nephritis (11%) and hematological abnormalities (30%) such as eosinophilia and circulating atypical monocytes.

Our patient exhibited classical findings of DRESS with mild hepatitis. Diagnosing DRESS is often difficult because it may be mistaken for a bacterial or viral infection such as scarlet fever or mononucleosis; however, the patient's titres made these diagnoses unlikely. Toxic shock syndrome shares similar features with DRESS (fever, diffuse rash and hepatitis); however, the patient did not meet the diagnostic criteria (no associated shock, and only two organ systems were involved: hepatic and gastrointestinal). Serum sickness-like reaction (hypersensitivity vasculitis) from cephalosporin use is a consideration, but our patient did not exhibit palpable purpura, symptom onset is usually more rapid (seven to 10 days after antigen exposure) and patients are usually older (older than 16 years).

The mechanisms of DRESS are controversial, possibly including abnormal detoxification of the reactive arene oxide drug metabolites. Reactivation of HHV-6 or HHV-7 has been described in a subset of patients with DRESS, sometimes with a more severe course. Because there is a familial tendency to develop DRESS, a positive family history should raise concern. An ethnic predisposition to DRESS associated with certain human leukocyte antigen subtypes may also exist.

Minimum investigations should include a complete blood count, liver enzymes test, urinalysis and baseline thyroid function tests. The latter should be rechecked two months later because drug-induced hypothyroidism resulting from drug hypersensitivity could be delayed. Other autoimmune complications, such as diabetes, may occur months or years after the acute phase. Hypotension and cardiac dysfunction have been described in adults, mostly associated with eosinophilia. An electrocardiogram and echocardiogram are recommended in patients with hypotension on presentation, especially if eosinophilia is present.

The priority in the management of DRESS is immediate discontinuation of the offending drug. Due to the high mortality rate, early consultation with an expert in drug hypersensitivity is recommended. Appropriate and timely supportive care that includes fluids and nutrition is essential because infection is a common mechanism of mortality for patients with significant cutaneous manifestations. Therapy with steroids, intravenous immunoglobulin or other immunosuppressants remains controversial and depends on the degree of systemic involvement. Definitive clinical trials to support aggressive treatment have not been performed. Despite discontinuation of the offending agent, most patients will continue to have symptoms for several days, and some will even deteriorate for weeks. Supportive therapy with topical corticosteroids and antipruritic medications may be helpful.

There is significant cross-sensitivity (40% to 80%) among the aromatic anticonvulsant drugs carbamazepine, phenytoin and phenobarbital. Therefore, it is imperative that patients who react to one of these drugs avoid further use of any of them. For patients who need to continue on anticonvulsant drugs, alternatives may include benzodiazepines and other nonaromatic anticonvulsant drugs such as gabapentin, levetiracetam and topiramate. Use of lamotrigine is controversial due to a small number of case reports implicating this drug in DRESS in patients who were already sensitive to other anticonvulsants. While valproic acid has also been implicated in a small number of DRESS cases, cross-reactivity with other anticonvulsants has not been observed.

CLINICAL PEARLS

- The classic triad seen in DRESS consists of rash, fever and systemic organ involvement (hepatitis is most common). Eosinophilia is common, but may be absent.
- DRESS is commonly caused by the aromatic anticonvulsants (phenytoin, carbamazepine and phenobarbital), sulpha drugs and allopurinol. It occurs two to eight weeks following initiation of therapy.
- DRESS is potentially fatal, and diagnosis may be delayed due to its similar presentation to various viral or bacterial infections.
- Treatment consists of immediate discontinuation of the offending drug and, in severe cases, administration of systemic corticosteroids.
- Cross-sensitivity is common and, therefore, other aromatic anticonvulsants should not be used. Alternatives may include benzodiazepines, gabapentin, levetiracetam and topiramate depending on the patient's underlying condition.

RECOMMENDED READING

1. Rieder MJ. Immune mediation of hypersensitivity adverse drug reactions: Implications for therapy. Expert Opin Drug Saf 2009;8:1-13.
2. Roujeau JC. Clinical heterogeneity of drug hypersensitivity. Toxicology. 2005;209:123-9.

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