

DRESS Syndrome Induced by Ranitidine



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A 16-year-old boy with a history of Tetralogy of Fallot underwent extended treatment for *Streptococcus mitis* infective endocarditis culminating in pulmonary valve replacement. Eighteen days postoperatively he developed a progressively extensive maculopapular exanthema with pronounced petechial and purpuric lesions across his limbs (Figure 1), facial edema, and mild mucosal involvement. He was febrile (39°C) and had palpable cervical lymphadenopathy. Over the following 72 hours he developed an eosinophilia ($0.8 \times 10^9/L$ [normal range $0.0-0.4 \times 10^9/L$]) with deranged liver function (alanine aminotransferase 100 IU/L [normal range 4-59 IU/L]), renal impairment (creatinine 116 $\mu\text{mol/L}$ [normal range 59-104 $\mu\text{mol/L}$]), and leukopenia (neutrophils $1.2 \times 10^9/L$ [normal range $1.5-7.0 \times 10^9/L$], lymphocytes $0.3 \times 10^9/L$ [normal range $1.2-3.5 \times 10^9/L$]). He had received an extensive list of medication in the 5 weeks preceding the onset of the exanthema, which included rifampicin, vancomycin, gentamicin, meropenem, and ceftriaxone (started in the first 2 weeks of admission), followed by enoxaparin, furosemide, spironolactone, temazepam, ibuprofen, paracetamol, and ranitidine (started 3 weeks before the onset of eruption). Histologic analysis of a biopsy specimen was consistent with a drug eruption (eosinophils and perivascular inflammatory infiltration). Blood cultures revealed no growth. Screening for autoantibodies, adenovirus, parvovirus, Epstein bar virus, herpes simplex virus, human herpes virus, and mycoplasma was all negative.

He was diagnosed with drug reaction with eosinophilia and systemic symptoms (DRESS) based on the RegiSCAR (European Registry of Severe Cutaneous Adverse Reaction) validation criteria¹ (Total score = 6 [Definite case], achieved from the following criteria: eosinophilia [1 point], rash extent >50% body surface area [1 point], rash suggesting DRESS [1 point], organ involvement [2 points], exclusion of other potential causes [1 point]). All medication was stopped 5 days after the onset of the eruption, and he was treated with topical steroids, which led to a full recovery after 3 weeks.

At our allergy clinic 9 months later, intradermal tests (IDT) with the diluted (0.9% NaCl) stock concentrations of rifampicin (1:10,000), vancomycin (1:100), gentamicin (1:100), meropenem (1:100), ceftriaxone (1:10), enoxaparin (1:10), and furosemide (1:100) were all negative on delayed reading (48 and 96 hours). We also performed patch testing (PT) using IQ Ultra chambers (Chemotechnique Diagnostics, Vellinge, Sweden) with temazepam (30% petrolatum [pet]) and spironolactone (30% pet), which was negative when read on day 2 (D2) and day 4 (D4), in accordance with the International Contact Dermatitis Research Group criteria. Delayed IDT with ranitidine (1:100 dilution) however produced a focal papulovesicular eruption at 96 hours (with a crescendo effect since 48 hours) (Figure 2). Immediate IDT was negative when read at 15 minutes. PT produced strong positive reactions to ranitidine (30% pet),



FIGURE 1. Extensive maculopapular exanthema with pronounced petechial and purpuric lesions.

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FIGURE 2. Positive delayed intradermal test with ranitidine (1:100 dilution) at 96 hours with a focal papulovesicular eruption.

ranitidine (undiluted solution), and cimetidine (30% pet) at D4 (Figure 3); all with crescendo effects since D2. Ten control subjects underwent IDT to ranitidine and PT to ranitidine and cimetidine, and the readings were all negative. We did not test paracetamol or ibuprofen as he had received them both after his eruption and tolerated them well. He was diagnosed with DRESS syndrome due to ranitidine based on the temporal relationship, clinical features (RegiSCAR criteria), biopsy outcome, and crucially the dual positive IDT and PT to ranitidine. He was advised to completely avoid all histamine H2-receptor antagonist medication.

DRESS syndrome is a severe cutaneous adverse reaction that carries a 10% mortality.² The pathogenesis is complex and is hypothesized to include delayed type IV (T-cell mediated) hypersensitivity, virus-drug interactions, and genetic associations (ie, human leukocyte antigen).³ It is commonly associated with antimicrobials, anticonvulsants, anti-inflammatory agents, and antivirals.² Ranitidine is an H2-receptor antagonist often used in the therapy of gastric and duodenal ulcer disease.⁴ Delayed-type hypersensitivity to ranitidine is rare but has been previously described⁴ (ie, acute generalized exanthematous pustulosis,⁵ toxic epidermal necrolysis⁶), as have IgE-mediated reactions to ranitidine (ie, anaphylaxis⁷). Here we describe the first reported case of DRESS syndrome due to ranitidine. We also demonstrate the novel finding of possible delayed-type cross-reactivity between ranitidine and cimetidine. It has previously been suggested that the furan ring is the main sensitizing structure in ranitidine.⁸ We highlight the importance of a comprehensive approach to investigating severe delayed-type hypersensitivity.

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FIGURE 3. Positive patch tests at day 4 to (A) ranitidine 30% pet (+++), (B) ranitidine undiluted solution (++), and (C) cimetidine 30% pet (++).

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