

Strontium ranelate-induced DRESS syndrome: first two case reports

A. P. Jonville-Béra*, B. Crickx, L. Aaron, I. Hartingh, E. Autret-Leca

Key words: drug rash with eosinophilia and systemic symptom syndrome; drug allergy; drug-induced; strontium ranelate.

We report the two first cases of drug rash with eosinophilia and systemic symptoms (DRESS) syndrome (1) induced by strontium ranelate, a new drug used to treat osteoporosis.

A new cause of DRESS syndrome.

A 78-year-old woman was prescribed strontium ranelate (SR). Ten days later, she developed a febrile, diffuse rash leading to the discontinuation of SR 2 days later and the prescription of prednisone (40 mg/day). She was admitted to hospital 8 days later with a generalized purplish rash, facial oedema and fever. Blood tests showed eosinophilia (7052/ml), hyperbasophilic lymphocytes (164/ml) and liver damage (AST 93 IU/l, ALT 202 IU/l, ALP 215 IU/l, GGT 301 IU/L). Skin biopsy showed a lymphohistiocytic infiltrate, with eosinophilia in the superficial dermis, and bone medulla was infiltrated with eosinophils (28%). Serological tests for hepatitis (B, C) were negative, as were autoantibody tests, blood and urine cultures. On the 18th day, the rash worsened with uveitis thus requiring an increase in the dose of prednisone. This led to improvement, but attempts to decrease corticoid dose led to the recurrence of DRESS syndrome.

A 69-year-old woman was prescribed cholecalciferol, calcium, percutaneous diclofenac, paracetamol and SR. Three

weeks later, she developed a rash. All the drugs were stopped and she was prescribed betamethasone. She was hospitalized 9 days later as a result of generalization of the rash with fever, facial oedema, enanthema, confusion, eosinophilia (712/ml) and liver damage (AST 53 IU/l, ALT 83 IU/l). She was given methylprednisolone (60 mg/day) and the rash quickly improved. Three days after stopping corticoid treatment, she had a generalized maculopapular rash with facial oedema, stomatitis, fever, kernicterus and confusion. Laboratory tests showed leucocytosis (18 800/mL), eosinophilia (2444/mL) and hyperbasophilic lymphocytes (546/mL) with serious liver (AST 641 IU/l, ALT 802 IU/l, ALP 2109 IU/l, GGT 1026 IU/L and PT 52%) and renal damage (CRE 292 µmol/l). Hepatic and vesicular ultrasound scans were normal. Blood cultures and serological tests (hepatitis A, B and C, HIV, CMV, toxoplasmosis, parvovirus B19 and HHV8) were negative. PCR (287 copies/ml) and serological tests for HHV6 were positive. The patient died of fulminant hepatitis 4 days later. Liver biopsy showed central and mediolobular necrosis, with polymorphous eosinophil cell-mediated inflammation.

Based on a recently published score (2) DRESS syndrome was considered 'probable' for the first case and 'definite' for the second, in which HHV6 infection was consistent with virus reactivation, which is thought to be involved in DRESS syndrome (3). Other causes of febrile eruption with eosinophilia and liver involvement were ruled out. A causality assessment of suspected adverse drug reactions (4) identified SR as the 'probable' cause for the first case, as the DRESS syndrome occurred within 33 days of treatment initiation (1). For the second case, SR, cholecalciferol, calcium, paracetamol and percutaneous diclofenac were all considered 'probable'. However, DRESS syndrome has

never been associated with these drugs and only one case has been reported for diclofenac *per os* (5).

To our knowledge, no case of DRESS syndrome associated with SR has ever been published, but eight other cases have been reported to French Pharmacovigilance Units. In seven patients, the eruption appeared within 3–6 weeks of the start of SR treatment. Clinical manifestations included skin lesions (8/8), eosinophilia (8/8), liver abnormalities (6/8), fever (5/8), lymph node enlargement (5/8), renal dysfunction (4/8), lung involvement (2/8) and neurological signs (2/8). Using RegiSCAR's score (2), DRESS was classified as 'definite' in two cases, 'probable' in four cases and 'possible' in two cases. These 10 cases, together with four others reported in Europe, have led the EMEA to inform healthcare professionals.

Because strontium, a divalent cation-like calcium, is not metabolized, it is possible that the 'ranelate' salt plays a role in the occurrence of this reaction. Despite Pernicova's recommendations (6), we believe that, if a patient develops a febrile rash, SR must be stopped.

*Department of Clinical Pharmacology
Regional Pharmacovigilance Unit
CHRU de Tours
2 boulevard Tonnelé
F-37044 Tours Cedex 09
France
Tel.: 0(33)2 47 478029
Fax: 0(33)2 47 473826
E-mail: jonville-bera@chu-tours.fr

Accepted for publication 24 September 2008
Allergy 2009
© 2009 The Authors
Journal compilation © 2009 Blackwell
Munksgaard
DOI: 10.1111/j.1398-9995.2009.01940.x

References

1. Bocquet H, Bagot M, Roujeau JC. Drug-induced pseudolymphoma and drug hypersensitivity syndrome (drug rash with eosinophilia and systemic symptoms: DRESS). *Semin Cutan Med Surg* 1996;**15**:250–257.
2. Kardaun SH, Sidoroff A, Valeyrie-Allanore L, Halevy S, Davidovici BB, Mockenhaupt M et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? *Br J Dermatol* 2007;**156**:575–611.
3. Descamps V, Valance A, Edlinger C, Fillet AM, Grossin M, Lebrun-Vignes B et al. Association of human herpesvirus 6 infection with drug reaction with eosinophilia and systemic symptoms. *Arch Dermatol* 2001;**137**:301–304.
4. Edwards I, Aronson J. Adverse drug reactions: definitions, diagnosis, and management. *Lancet* 2000;**356**:1255–1259.
5. Chiou CC, Chung WH, Hung SI, Yang LC, Hong HS. Fulminant type 1 diabetes mellitus caused by drug hypersensitivity syndrome with human herpesvirus 6 infection. *J Am Acad Dermatol* 2006;**54**:S14–S17.
6. Pernicova I, Middleton ET, Aye M. Rash, strontium ranelate and DRESS syndrome put into perspective. *European Medicine Agency on the alert. Osteoporos Int* 2008;**19**:1811–1812.