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Strontium ranelate-induced DRESS syndrome: first two case reports

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

A new cause of DRESS syndrome.

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 78-year-old woman was prescribed strontium ralenate (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 'ralenate' 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.

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Tomato atopy patch test in adult atopic dermatitis: diagnostic value and comparison among different methods

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Key words: atopic eczema/dermatitis syndrome; ready-to-use atopy patch test; repeated open food challenge; skin prick test; tomato atopy patch test.

Atopic dermatitis, defined atopic eczema/dermatitis syndrome (AEDS) according to the revised EAACI/GA^{2}LEN nomenclature (1), is a chronic inflammatory skin disease characterized by recurrent intense itch. The role of food allergy in promoting and maintaining the eczematous lesions in AEDS is controversial. Several studies outline that AEDS in childhood can be exacerbated by the intake of common foods such as hen's eggs, cow's milk, wheat, soy and peanuts (2), while the role of offending foods in the exacerbation of AEDS in adult patients is still unknown. Although in adolescents and in adults, the worsening of eczema is poorly influenced by food ingestion, pollen-associated food (i.e. apple, tomato, citrus fruits, tree nuts and peanuts) can play a key role in the exacerbation of AEDS in 15% of adult patients (3–5). Eczematous reactions to food can be diagnosed through accurate diagnostic procedures (*in vivo* or *in vitro* detection of specific IgE) taking into account the patient's history, degree and clinical relevance of sensitization proved by oral food challenges (6). In the last years, the atopy patch test (APT) was considered an additional tool in the diagnosis of non-IgE-mediated food allergy in patients who experienced dermatitis after the intake of offending food (7–9). In particular, APT may play a key role in the identification of food allergy in AEDS in case of: (i) absence of significant specific IgE levels or negative response to skin prick test (SPT) in food symptomatic patients; (ii) severe-persistent AEDS without trigger factors and (iii) multiple IgE sensitizations to foods without clinical relevance (6).

Tomato atopy patch test in adult atopic dermatitis.

The aims of our study were to assess: (i) the role of tomato ingestion correlating the results of SPT and tomato APT with the repeated open food challenge (ROFC) employing fresh tomato and (ii) the performances of APT with fresh tomato *vs* standardized commercial tomato allergens in petrolatum, in an adult population from Southern Italy affected by persistent AEDS.

A total of 98 patients with persistent mild-to-severe AEDS (42 males and 56 females) aged 24–48 years (mean age 34.7 years) were enrolled in the study. The diagnosis of atopic eczema was made according to Hanifin and Rajka criteria (10), while the severity of eczema was scored by the severity Scoring index atopic dermatitis (SCORAD) (11), which includes topography items (affected skin area), intensity criteria (erythema, oedema, crusts, excoriations, lichenification and xerosis) and subjective evaluations like intensity of itch and loss of sleep. According to severity of AEDS, 38 patients suffered from mild AEDS (SCORAD $<$ 25 points), 48 from moderate AEDS (SCORAD between 25 and 50 points) and 12 from severe AEDS (SCORAD $>$ 50 points).

All patients had suspended any treatment with systemic corticosteroids or cyclosporine 4 months before the enrolment, while the administration of systemic antihistamines was allowed until 7 days before the beginning of the study. Moreover, the application of topical corticosteroids or anti-inflammatory drugs was possible until 3 weeks before the recruitment. All patients excluded from their diet tomato, apple, soy, celery, wheat, citrus fruits and nuts for 4 weeks. The evaluation of AEDS clinical status was made at the enrolment, after elimination diet and after tomato challenge. Patients with positive clinical history for immediate reactions to foods were not included.

Skin prick test with tomato was performed using commercial food extracts from Stallergènes, Milan, Italy. Positive and negative controls were histamine dihydrochloride (10 mg/ml) and glycerinated saline respectively. The readings were interpreted according to the European Academy of Allergology and Clinical Immunology-Subcommittee (EAACI) on allergen standardization and skin tests (12). The response was considered positive if the wheal diameter was more than 3 mm, bigger than that provoked by the negative control.

Tomato-specific IgE was detected using the ImmunoCAP System radioimmunoassay (Phadia, Milan, Italy). Patients with specific IgE level $>$ 0.35 kU/l (detection limit value of the CAP System) were considered sensitized to allergen.

The APT was performed in all patients with two different methods at the same time. Each patient was tested on the right back skin without AEDS lesions with both an extemporaneous preparation of fresh whipped tomato APT (APTf) (20 mg) applied on a filter paper covered with IQ Chambers (Chemotechnique Diagnostics, Sweden) both a tomato ready-to-use APT (APTr) (Atopy line 1 Euromedical S.r.l. Calolziocorte, Milan, Italy) placed on the IQ Chambers. IQ Chamber consists of inert square polyethylene foam chambers attached to a hypoallergenic porous tape (Scanpor tape). IQ chambers for APTr are with already integrated tomato allergens at a standardized concentration of 20% in petrolatum with a variability of $\pm$3%

