

DRESS syndrome induced by sodium meglumine ioxitalamate

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Key words: adverse drug reaction; DRESS syndrome; iodinated contrast media; patch test; sodium meglumine ioxitalamate.

We report the first case of DRESS (drug rush with eosinophilia and systemic symptoms) syndrome induced by sodium meglumine ioxitalamate. Immediate reactions are the more frequent adverse reactions to iodinated contrast media (ICM) (1–6). Occurrence of delayed hypersensitivity reactions caused by these products had been more rarely reported (1–6). We report a case of DRESS syndrome induced by sodium meglumine ioxitalamate (Telebrix 35[®]; Guerbet, Paris, France).

A 71-year-old woman was hospitalized for thoracic pain and dyspnea. Coronary angiography was performed with sodium meglumine ioxitalamate (Telebrix 35[®]). The conclusion was thrombosis of the anterior interventricular artery leading to the diagnosis of an antero-septal myocardial infarction. Treatment with isosorbide dinitrate (Risordan[®]; Sanofi-Aventis, Paris, France), chlorhydrate of propranolol (Avlocardyl[®]; Bristol-Myers Squibb, Paris, France), acetylsalicylic acid (Aspirine[®]; Siphat, Tunis, Tunisia), and clopidogrel hydrogen sulfate (Plavix[®]; Astra Zeneca, Paris, France) was started. The days following the coronary angiography were without incidents. Seven months after, the patient underwent a transluminal angioplasty with a stent installation, which included the injection of the same ICM (Telebrix 35[®]). Two days later, the patient had developed a pruritic maculo-papular rash, fever (38.5°), and oliguria (diuresis within 100 cc/24 heures). Laboratory investigations revealed a creatinine rise (266 µmol/l) and eosinophilia (1600

A rare cause of DRESS syndrome.

elements/mm³). Hepatic enzymes were within normal limits. Blood cultures were negative and the C-reactive protein level was within normal limits. A skin biopsy showed perivascular infiltration of lymphocytes accompanied with dermal infiltrates of eosinophils. Given the association of fever, rash, eosinophilia and the renal attack, the diagnosis of DRESS syndrome was established and sodium meglumine ioxitalamate was suspected to be the trigger agent. As they were started 7 months ago, the other treatments received by the patient were continued. Four days after, the rash intensified, renal insufficiency aggravated (creatinine = 411 µmol/l) and eosinophilia increased to 1800 elements/mm³. Fever and rash were completely resolved within 17 days with normalization of creatinine level and eosinophilia count. Six weeks after complete resolution, the patient was patch tested with European standard series, and sodium meglumine ioxitalamate (30% in water and undiluted). Reactions were evaluated at D2 and D3 according to ICDRG guidelines. Positive reactions (+ +) were seen at D2 and D3 to sodium meglumine ioxitalamate (30% in water and undiluted). The same patch tests gave negative results in nine healthy control subjects. Thus, the diagnosis of DRESS syndrome induced by sodium meglumine ioxitalamate was confirmed.

Late adverse reactions with ICM occurred from 1 h to 2 days after administration but have been reported to occur up to 7 days after administration (2, 3). They include rash, urticaria or eczema, more rarely, Stevens-Johnson or Lyell syndromes, even fixed drug eruption or vasculitis (1–6). Most of these skin eruptions appear to be T-cell mediated allergic reactions as shown by the frequently reported positive patch tests and delayed intradermal tests to the ICM (4–6). DRESS syndrome is a severe, acute drug reaction, defined by the presence of fever, skin eruption and systemic findings including enlarged lymph nodes, abnormal liver function, renal impairment, pulmonary or cardiac infiltrates along with hematological abnormalities, mainly hypereosinophilia and lymphocytosis (7, 8). In our patient, the diagnosis of DRESS syndrome was definite according to the new RegiSCAR group criteria (9). Iodinated contrast media-

induced DRESS syndromes are rarely reported (10–12). Kanny et al. (11) reported in 2005, four ICM-induced DRESS syndromes that were triggered by Iohexol, Iobitridol and Ioxaglate. In these four cases of DRESS, patch tests with ICM were positive only two times out of four. To the best of our knowledge, apart from these cases, only another case had been reported in the literature (12). Our case is considered the first case reported of DRESS syndrome induced by sodium meglumine ioxitalamate.

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Delayed hypersensitivity to acylureidopenicillins: a case report

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Key words: intradermal test; mezlocillin; patch test; piperacillin; selective delayed hypersensitivity.

Like mezlocillin, piperacillin is a wide-spectrum acylureidopenicillin, which can provoke all kinds of nonimmediate reactions, particularly maculopapular rashes (1). In some of the latter, a cell-mediated pathogenic mechanism

Selective hypersensitivity to acylureidopenicillins diagnosed on the basis of responses to both *in vitro* and *in vivo* tests.

has been diagnosed on the basis of patch-test and/or delayed-reading intradermal test positivity (2–5). In particular, Warrington et al. (2) and Cabañas et al. (3) described two different patients who had experienced maculopapular eruptions associated with piperacillin treatments, one of whom presented delayed-reading intradermal test positivity to piperacillin and the other patch-test positivity to the same drug. Both of them displayed allergologic-test negativity to the classic penicillin determinants, as well as to ampicillin and amoxicillin. Therefore, their reactions were probably caused by a selective sensitization to piperacillin; however, these patients were not challenged with negative β -lactams. In 2002, our group (4) described two cases of cell-mediated hypersensitivity that presented delayed intradermal-test and patch-test positivity to piperacillin, as well as to ampicillin and amoxicillin. These patients tolerated benzyl-penicillin and cefaclor, indicating that cross-reactivity between piperacillin and aminopenicillins was probably because of structures shared by the side-chain groups.

We present the case of a 50-year-old woman with a history of pruriginous maculopapular rash and facial angioedema that occurred on the 3rd day of treatment with piperacillin (Avocin; Wyeth Lederle SPA, Aprilia, Italy). She had undergone herniotomy for umbilical hernia and 2 g/day of Avocin were administered intramuscularly during the postoperative period. The drug was immediately discontinued and the symptoms resolved completely after 4 days of corticosteroid therapy (6-methylprednisolone intravenously, 40 mg daily). She was not taking any other drugs at the time of the reaction.

Eight years later, the patient was referred to our allergy clinic and underwent an allergologic evaluation, according to the diagnostic algorithm devised by the European Network for Drug Allergy (ENDA) (6), which includes patch tests with benzyl-penicillin, ampicillin, amoxicillin and piperacillin (5% in petrolatum; F.I.R.M.A., Florence, Italy), as well as skin tests with the classic penicillin reagents – penicilloyl-polylysine (DAPTM, Diater, Madrid, Spain), minor determinant mixture (DAPTM; benzyl-

penicillin, sodium benzyl-penicilloate and benzyl-penicillic acid), and benzyl-penicillin (Pharmacia, Milan, Italy) – in the first evaluation. The final concentrations of the penicillin reagents were, respectively, 1.07×10^{-2} mmol/l, 1.5 mmol/l and 10 000 IU/ml. No immediate reactions to skin tests were observed. In the second evaluation, 2 days later, we performed patch-test and late-intradermal-test readings, as well as skin tests with semi-synthetic penicillins. A positive response (+ + +) to the piperacillin patch test was observed. Ampicillin (Amplital; Pfizer, Latina, Italy) and amoxicillin (Amoxil; Glaxo Smith Kline, Middlesex, UK) were tested at concentrations of 1 and 20 mg/ml in normal saline, while piperacillin (Avocin) was tested only at 1 mg/ml, because of the patch-test positivity. No immediate reactions were observed, while 10 h later, an indurated, erythematous lesion approximately 10 mm in diameter with vesicles developed at the piperacillin injection site. Such reaction was still present at the 48- and 72-h readings.

Two weeks later, we performed skin tests with mezlocillin (Baypen, Bayer S.p.A., Milan) at a concentration of 1 mg/ml, cefaclor (Panacef, Aleas S.p.A., Milan) and ceftriaxone (Rocefin, Roche, Milan) at 2 mg/ml of normal saline, as well as patch tests with mezlocillin and the above-mentioned cephalosporins (5% in petrolatum, F.I.R.M.A.). The patient displayed skin-test negative results to cephalosporins, while 48 h later, she presented both delayed intradermal-test and patch-test positivity (+ +) to mezlocillin.

We also carried out lymphocyte transformation tests (LTT) according to Nyfeler and Pichler (7). Benzyl-penicillin, ampicillin, amoxicillin, piperacillin, mezlocillin, cefaclor and ceftriaxone were added to the medium at concentrations ranging from 2 to 500 μ g/ml. Tetanus toxoid (Istituto Berna, Barcellona, Spain) was used as a control antigen. The stimulation index (SI) was calculated as counts per minutes of antigen-containing cultures divided by counts per minute of control cultures (cultures without antigen). A SI higher than 2.0 was interpreted as a positive result. The LTT was also carried out in five subjects who had previously tolerated piperacillin. None of