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CLINICAL REPORT

Drug-induced Eosinophilia and Multisystemic Failure with Positive Patch-Test Reaction to Spironolactone: DRESS Syndrome

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We report the case of a 58-year-old man who suffered from a generalized and intolerable itching one month after starting treatment with colchicine, amiodarone, perindopril, allopurinol and spironolactone. From the start of treatment he had progressively developed erythroderma, fever, anorexia and prostration, oedema of both hands and face, hypereosinophilia (42%; 5810 eosinophils/mm^3), hepatic failure (including cholestatic jaundice, cytolysis, coagulation abnormalities and hypoproteinaemia), exocrine pancreatic failure (with severe steatorrhoea), renal failure, metabolic acidosis, aggravation of pre-existing cardiac insufficiency and oedema of the lower extremities. All medications were stopped and the condition improved slowly until complete remission was reached 4 months later. Patch-testing was performed, including the various drugs. All the tests (including components of the vehicles) were negative, except for spironolactone, which gave a strong positive reaction. Ten controls in healthy volunteers were negative. The diagnosis of drug rash with eosinophilia and systemic symptoms (DRESS) induced by spironolactone was made. This is the first report of DRESS due to spironolactone. ***Key words: DRESS; drug-induced eosinophilia; hepatic insufficiency hypersensitivity; spironolactone.***

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Drug hypersensitivity syndrome, initially described in relation to anticonvulsants, is a severe, potentially life-threatening, drug reaction. The eponym "DRESS syndrome" has been proposed, meaning "drug rash with eosinophilia and systemic symptoms".

We report a typical case of DRESS syndrome. Allopurinol was initially suspected, but clinical evolution and patch tests modified the critical odds assessment. There is strong evidence that spironolactone is involved in the occurrence of the disease.

CASE REPORT

A 58-year-old man presented in August 1999 with an acute gout attack (first episode). An atrial fibrillation was discovered at the same time, with a decreased ejection fraction. Colchicine was started on 1 September, along with amiodarone and perindopril. Spironolactone was introduced later (3 September). Colchicine was progressively replaced by allopurinol (from 5 September) and stopped on 20 September.

From 28 September the patient noticed diffuse itching, worsening from day to day, and a generalized rash appeared a few days later (Fig. 1). Blood examination revealed moderate eosinophilia (7%) and hepatic cytolysis. The patient was hospitalized on 12 October. The skin was diffusely red brownish and infiltrated, and the face oedematous and exudative, with yellowish small crusts. The backs of the hands and the lower extremities were swollen (Fig. 2). Many large and small joints were painful. Body weight increased steadily (12 kg) in one week. Fever was present

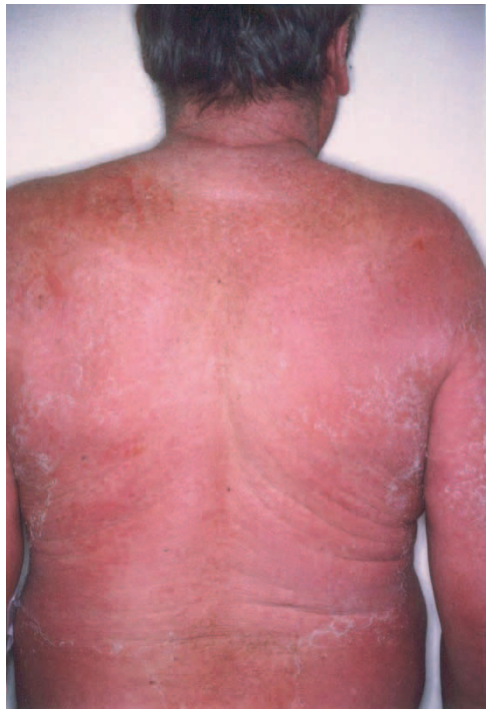

Fig. 1. Diffuse erythema with subsequent desquamation.

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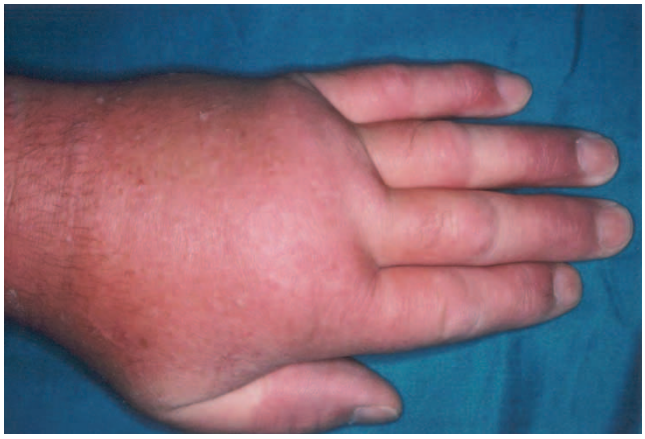

Fig. 2. Erythema and oedema of the extremities.

(38.2°C). Conjunctivae were subicteric. Axillary and inguinal small lymph nodes were noted. The patient was apathetic and anorexic; he gave a description of generalized malaise and extreme tiredness. Itching was unbearable. Eosinophil count was increased to 19%.

A skin biopsy displayed the following features: numerous cytoid bodies (Civatte's bodies) isolated or clumped in lower epidermis, liquefactive alteration of epidermal basal cells, perivascular lymphocytic infiltrate limited to upper dermis, with exocytosis of inflammatory cells into the epidermis, all features highly suggestive of drug eruption.

Amiodarone and/or allopurinol were initially suspected and removed on 12 October. In the following days, hepatic failure progressed: cytolysis (lactate dehydrogenase to 4.5 times above the upper limit of normal value, gammaglutamyl transpeptidase 13×, SGOT 7.5×, SGPT 12×, alkaline phosphatase 45×), cholestasis (conjunctival jaundice, dark urine, white feces, total bilirubin 3.5 mg/dL (N: 0.3–1.2), direct bilirubin 3 mg/dL), coagulation abnormalities (PTT 1/3× without any anticoagulant therapy). Exocrine pancreatic function was also abnormal, with amylases 3×, lipases 4×, diarrhoea and severe steatorrhoea. The total serum protein level count was decreased to 4.60 g/dL (N: 6.5–8), with 51.4% of albumin (N: 58–68). Kidney failure was evident, with plasma urea increased to 148 mg/dL (N: 15–50) and creatinine to 1.9 mg/dL (N: 0.8–1.3). Metabolic acidosis was obvious for a few days (pO_2 86 mmHg, pCO_2 25 mmHg, base excess −12, total CO_2 11.5 mmol/L).

Additional investigations: the dosage of amiodarone was normal. Blood examination revealed no atypical lymphocytes. Viral serologies were negative for cytomegalovirus, rubella, hepatitis B and C, Coxsackie B3, HIV and HTLV1; IgG levels were positive for Epstein-Barr virus, HHV6 (human herpesvirus 6), parvovirus B19 and hepatitis A virus. Feces samples showed no parasites. Thyroid function was normal. Abdominal echography and chest radiographs were normal.

Perindopril and spironolactone were removed on 22 October. Liver and pancreas functions normalized but itching remained severe. At the end of October, because of the increasing eosinophil count to 42.2% (5810 eosinophils/mm^3), oral corticosteroid treatment was started (methylprednisolone 0.66 mg kg^{-1}), leading to a drop in the eosinophil count to 0.9% (70 eosinophils/mm^3) during the next few days. Corticosteroid maintenance therapy did not prevent recurrences of moderate eosinophilia. The patient anticipated these recurrences, since they were linked with itching, erythema and oedema. Improvement in general condition was noticeable one month later, and the patient was allowed to go home after 7 weeks. The complete cure was slow; corticosteroid therapy was gradually reduced and stopped after 3 months. No recurrence was observed after one year of follow-up. Colchicine was reintroduced without problem.

Eight weeks after complete cure, patch-testing was performed with the five recently introduced drugs (tablets were crushed and incorporated at 10%, 20% and 30% in both white petrolatum and saline solution). The patch tests were removed at 48 h and read at 72 h and 96 h – the results as follows: colchicine, allopurinol, perindopril and amiodarone (−); spironolactone (+++), according to ICDRG (Fig. 3). Patch tests to spironolactone were negative in 10 healthy volunteers. In a second step, patch tests were conducted in our patient with the various ingredients incorporated in Aldactone® tablets, at 1% and 10% in petrolatum,

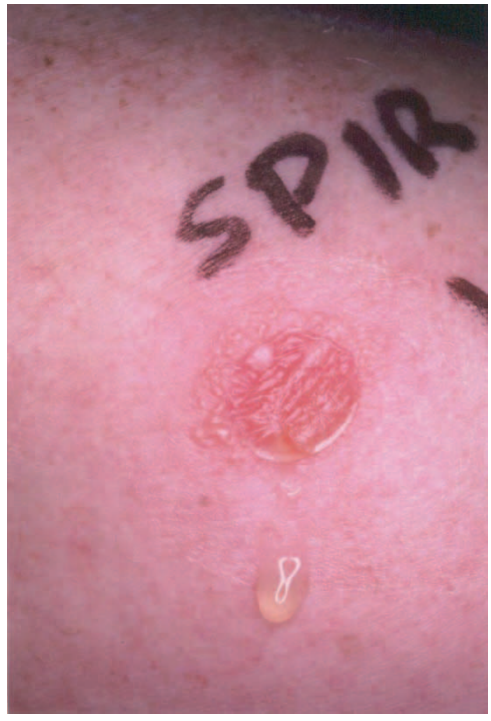

Fig. 3. Positive patch test to spironolactone (10% in petrolatum).

including spironolactone (analytical grade). All tests were negative, except spironolactone (++).

DISCUSSION

The present case was considered a severe form of ''drug-induced hypersensitivity syndrome DRESS''. Clinical aspects and history are typical: itching, erythema, facial oedema and crusts, altered general condition, visceral involvement (hepatic, renal, pancreatic), with hypereosinophilia, 4 weeks after the introduction of new drugs (1).

The pathophysiological pathways are poorly understood (2). Detoxification defects have been implicated, associated with an inherited component. Slow acetylation is considered a risk factor only for aromatic amines like sulfonamide antimicrobials. The role of a viral coinfection is suspected (specifically, a reactivation of HHV6).

The overall mortality in DRESS is about 10%, death occurring in patients with severe multiorgan involvement or previously altered general condition. The most frequently incriminated drugs are anticonvulsants, sulfonamides, dapsone, allopurinol, minocycline and gold salts. No treatment exists when the responsible drug has been discontinued. If the patient takes more than one drug, it is prudent to remove all of them. When some drugs are absolutely necessary, they should be replaced by unchemically related substitutes. The follow-up is important: recurrences are possible for some weeks or months. Nursing is symptomatic – against itching and to preserve vital functions. Corticosteroids decrease eosinophilia and improve the comfort of the patient, but the risk/benefit ratio is not clear (3): systemic steroids may be life-saving in some types of visceral involvement (interstitial pneumonitis, nephritis, myocarditis, etc.), but steroids increase the risk of recurrence, perhaps by promoting HHV6 reactivation and chronicity. Tapering of systemic steroids should be progressive.

An important step in differential diagnosis is to exclude malignant hemopathies. Erythroderma, deterioration of general condition, blood cell count abnormalities and frequent atypical cells can be seen in both conditions.

In the present observation, correct diagnosis was delayed, and spironolactone was not suspected at first as the culprit drug. This can partially explain the severity and duration of symptoms. Most of the symptoms were improved after spironolactone discontinuation, but eosinophil count continued to increase. Each hypereosinophilic recurrence was accompanied by itch, oedema, recurrence of atrial fibrillation and renal failure. It is well known in DRESS that eosinophilia may persist for some weeks or months, with spontaneous or steroid-induced variations. Paroxystic atrial fibrillation was pre-existing; recurrence was provoked by volaemic changes. Cardiac echography did not reveal any specific cardiac lesion. Increased urea and creatinine levels could be explained by metabolic alterations as well as by drug-induced nephritis.

Spironolactone is an aldosterone antagonist with antiandrogenic activity. It is used for cardiac failure and topically in some forms of acne. The cutaneous adverse effects are rare; in one study, papulo-erythematous eruption was observed in 0.5% of treated patients (4). Spironolactone was also reported to induce erythema annulare centrifugum (5, 6), lichenoid eruption (7, 8), lupus erythematosus (9), vasculitis, Raynaud's phenomenon and facial pigmentation (10). Some observations are of particular interest: one patient presenting erythema multiforme was successfully desensitized by the progressive reintroduction of spironolactone (11). In another report, two patients suffered from a maculopapular exanthema with hypereosinophilia and severe itching. One of them was submitted to an oral provocation test with spironolactone, which was positive (12). Gupta et al. also reported one case of maculopapular eruption with itch, oedema of the hands and palmar dysaesthesia (no blood examination mentioned) with a positive oral provocation test to spironolactone (10).

Allergic contact dermatitis to spironolactone is well documented, either after topical use or occupational manipulation during chemical synthesis of the drug (13–19). Patch tests are positive to spironolactone (1% or 2% in petrolatum); patch testing with Aldactone® tablets as such is liable to provoke irritant reactions.

In our patient, intrinsic imputability was considered similar for amiodarone, allopurinol, perindopril and spironolactone. However, extrinsic imputability (reference's data) listed allopurinol on the first line. Subsequently, odds assessment was re-evaluated on clinical grounds, including evolution of the disease. Patch test results also had an impact on the final diagnosis: with the Bayesian approach, the prior odds for spironolactone are moved up, and the negative result has some impact on moving the allopurinol odds down. Odds assessment is important when evaluating which drug might be removed during management and, finally, which drug should be avoided in the future.

Patch test specificity is not 100%. An oral provocation test is considered the ultimate proof, but is not ethically recommended in DRESS syndrome. Positive patch tests to the culprit drug are probably a good compromise; this approach has been advocated in previous reports on DRESS syndrome (2, 20).

In conclusion, spironolactone can be added to the list of drugs inducing DRESS syndrome. Systematic use of patch testing in all cases of DRESS syndrome would provide more information about their relevance.

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