Hydrochlorothiazide-induced Acute Generalized Exanthematous Pustulosis

Sir,

Hydrochlorothiazide is a thiazide diuretic widely used in adult high blood pressure and found in more than 10 pharmaceutical preparations. A few drug reactions have already been described with thiazide diuretics, including vasculitis, phototoxic/allergic eruption and erythema multiforme (1). No case of sulfonamide thiazide-induced acute generalized exanthematous pustulosis (AGEP) has been reported to date.

CASE REPORT

A 70-year-old woman was hospitalized for an acute febrile cutaneous eruption that had started 4 days earlier, localized first on the trunk and rapidly extending. Onset of fever preceded the eruption by 2 days She was nauseous, with vomiting and shivering. Skin examination revealed generalized diffuse macular erythema (on about 25% of the body surface area) associated with slight oedema and confluence of many non-follicular and superficial pustules. The eruption was predominantly located at the proximal skin folds and was followed by pinpoint desquamation in the axillary folds. The Nikolsky sign was absent. There was no mucous membrane involvement. She had conjunctival jaundice and the right hypochondrium was palpation sensitive. Blood tests demonstrated leukocytosis (14,200/mm^3 with 284 eosinophils/mm^3 and 12,600 neutrophils/mm^3), abnormal liver function tests (transaminase levels 4 times the normal value) and hepatic cholestasis (gamma-glutamyltransferase 186 IU/l, normal value < 20 IU/l, alkaline phosphatase level 205 IU/l, normal value < 145 IU/l). The serum creatinine level was normal. Skin biopsy revealed spongiform subcorneal pustules, dermal oedema and eosinophil-rich perivascular infiltrate. She had no history of psoriasis. The patient had been taking aspirin, simvastatin, clonazepam, pentoxifyllin and fusinopril for several years. Because of persistent high blood pressure despite fusinopril therapy, she had started taking hydrochlorothiazide 6 days before the eruption occurred. The outcome was favourable a few days after stopping hydrochlorothiazide (she continued to take the other drugs), with complete disappearance of the pustules and normalization of the liver function tests in 6 days. The patient refused diagnostic patch-testing.

DISCUSSION

AGEP was diagnosed using the criteria of Roujeau et al. (2). The patient fulfilled all of the criteria: clinical criteria (erythematous and oedematous rash with numerous pustules of less than 5 mm in diameter, hyperthermia and complete recovery in less than 15 days), biological criteria (neutrophilia) and histological criteria (dermal oedema, perivascular eosinophil infiltrate, keratinocyte necrosis and intraepidermal pustules). Hypersensitivity syndrome might have been discussed in this case because of the initial abnormal liver function tests. Absence of eosinophilia, atypical lymphocytes and rapidly favourable evolution excluded this diagnosis. Moreover, among 63 patients with AGEP in the series by Roujeau et al., 7 showed moderately increased transaminase levels (2).

The most frequent drugs inducing AGEP are antibiotics [87% in the series by Roujeau et al. (2)]. The interval to cutaneous manifestations is then usually shorter than 24 h. However, for other culprit drugs the interval is about 18 days (3); in our case the interval was 6 days. According to the French criteria of causality (4), the imputability of hydrochlorothiazide is high (I3: probable causality). Antibacterial sulfonamides are frequently responsible for severe cutaneous adverse drug reactions. Nevertheless, only 1 case of AGEP has previously been reported with antibacterial sulfonamide (5), but never with a diuretic sulfonamide. Moreover, in a case–control study using data obtained through surveillance networks in France, Germany, Italy and Portugal to quantify the risks of Stevens–Johnson syndrome or toxic epidermal necrolysis associated with the use of specific drugs, there was a high risk of toxic epidermal necrolysis with antibacterial sulfonamides but no excess risk with other sulfonamides such as sulfonylureas or thiazide diuretics (6). This case is therefore the first case of thiazide-induced AGEP.

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