Fluconazole-induced Stevens-Johnson Syndrome in a HIV-negative Patient

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Sir,

Stevens-Johnson syndrome (SJS) is a rare and severe mucocutaneous disorder, most frequently caused by systemic drugs, with an incidence of 1–6 cases per million person-years (1). It is characterized clinically by a maculopapular and bullous eruption with epidermal necrosis and detachment, mucosal ulcers and erosions and constitutional signs and symptoms. SJS and toxic epidermal necrolysis (TEN) are presently regarded as clinical forms of the same disorder that share common aetiopathogenetic factors but mainly differ in: (*i*) the extent of epidermal detachment (SJS < 10% body surface vs. TEN > 30%); (*ii*) the prognosis (SJS = good; TEN = poor); and (*iii*) the mortality rate (SJS < 5% vs. TEN = 30–40%) (2, 3).

Although the exact pathogenetic mechanisms of SJS and TEN at the molecular and cellular level remain to be elucidated, there is evidence suggesting a cytotoxic cell immune response against keratinocytes that is induced by various drugs, mostly sulphonamides, allopurinol, phenytoine, phenobarbital, carbamazepine, lamotrigine, non-steroidal anti-inflammatory drugs and nevirapine (4). Since it is of essential importance to recognize and report drugs capable of inducing severe adverse reactions, we describe herein the first case of SJS occurring in a HIV-negative patient during oral fluconazole treatment.

CASE REPORT

A 50-year-old Caucasian woman was admitted to the Department of Dermatology at the University of Patras Medical Center with a 3-day history of skin and mucosal lesions accompanied by high fever and malaise. The cutaneous manifestations had developed one week after the onset of treatment of vaginal candidiasis with 200 mg/day oral fluconazole (Flucodrug caps; Med-One, Athens, Greece). Apart from fluconazole, the patient had received no other medication and had no history or evidence of infectious, autoimmune or neoplastic disorders. Physical examination of the patient on admission revealed a confluent erythematoviolaceous, maculopapular and focally bullous pruritic skin rash with large numbers of targeted lesions over her face, upper trunk and the extremities. In a small area on her back, epidermal detachment was clearly seen (Fig. 1A). There were superficial ulcers and erosions in the oral mucosae, erosions and crusts on her oedematous lips (Fig. 1B) and a severe conjunctivitis. Blisters and epidermal detachment affected about 9% of the patient's body surface. Apart from a vaginal culture positive for *Candida albicans*, all haematological, biochemical, immunological and serological investigations (including tests for HSV, HIV 1 & 2, hepatitis A, B and C, *Toxoplasma*, Epstein Barr virus,

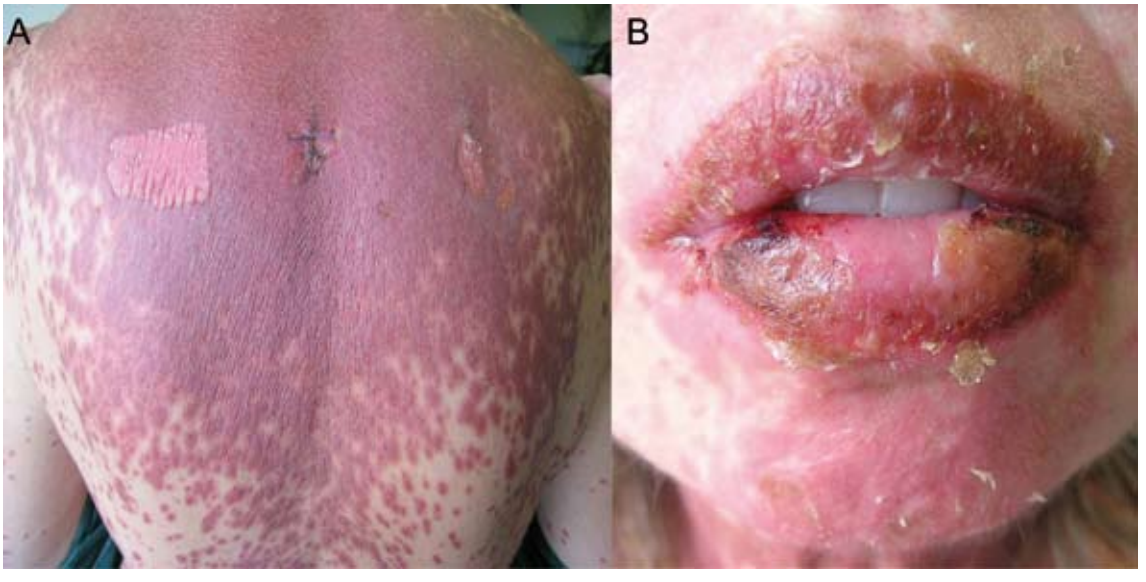

Fig. 1. (A) Confluent maculopapular rash with focal epidermal detachment. (B) Erosions and crusts on the oedematous lips.

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CMV, *Mycoplasma* and *Borrelia burgdorferi*) were either negative or within normal limits. Histological examination of skin biopsy specimens revealed a marked epidermal keratinocyte necrosis, subepidermal splits and a mostly mononuclear perivascular inflammatory cell infiltrate. These histological features were consistent with SJS and confirmed the clinical diagnosis of this syndrome.

Fluconazole was discontinued on admission, and treatment with antiseptic eye drops and oral and skin washings was instituted. Additionally, the patient received intravenous methylprednisolone at a dose of 120 mg/day for 3 days, which was gradually decreased over a period of 3 weeks. The mucocutaneous lesions revealed a rapid therapeutic response and completely resolved within 4 weeks. Vaginal candidiasis was successfully treated with a topical amphotericin suspension (Fungizone; Bristol-Myers Squibb, Athens, Greece).

DISCUSSION

Fluconazole is a new synthetic triazole antifungal drug known to selectively inhibit fungal cytochrome P450 enzyme 14α-demethylase (5), thus preventing the conversion of lanosterol to ergosterol (essential component of the fungal cytoplasmic membrane) and causing accumulation of 14α-methyl sterols. It is widely used in the treatment of cutaneous and systemic infections caused by *Candida species* and *Cryptococcus neoformans*, particularly in immunosuppressed patients. The adverse reactions to fluconazole reported so far include haematological, neurological, metabolic, hepatic, gastrointestinal, endocrine and cutaneous side-effects (5). Mucocutaneous adverse reactions to fluconazole are usually mild and include pruritus, urticaria, maculopapular eruptions, fixed drug eruption, alopecia, exfoliative dermatitis, angioedema and purpura. Only one case of SJS (6) and one of TEN (7) definitely caused by fluconazole have been described previously, both in patients with HIV infection. Since fluconazole was the only drug being administered to our patient when the mucocutaneous lesions first appeared and all other aetiological factors were ruled out, there is no doubt that this drug was responsible for the occurrence of SJS.

To our knowledge, the case of SJS presented here is the first to be reported during fluconazole administration to a HIV-negative patient. SJS is a potentially life-threatening disorder whose successful management depends mainly on early diagnosis and discontinuation of the responsible drug. We suggest, therefore, that fluconazole should be considered as one of the risk drugs capable of causing SJS, not only in HIV-positive patients, who are more prone to develop drug eruptions, possibly because of their immune disturbance (8), but also in immunocompetent patients.

The authors declare no conflicts of interest.

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