Fixed drug eruption caused by fluconazole—An underdiagnosed but recurrent problem

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Fixed drug eruptions (FDEs) account for ~16% of all cutaneous drug reactions. The FDE is characterized by recurrence at the same site after repeated exposure to a causative drug.[1,2] The current concept of the pathogenesis focuses on a specific $CD8^-$ T cell-mediated delayed-type hypersensitivity reaction resulting from local reactivation of memory T lymphocytes in epidermal and dermal tissues.[3]

CASE REPORT

A 66-year-old woman was referred to our outpatient allergy clinic because of a possible drug hypersensitivity reaction after she had taken a single 150-mg fluconazole tablet for tinea pedis 3 months previously. She reported burning, macular erythematous lesions on both lower legs that resolved within 7 days without any treatment, leaving faint post-inflammatory hyperpigmentation. On further inquiry, she recalled a history of similar episodes in the same location approximately 1 and 2 years previously.

The intermittent nature of the flares and the macular hyperpigmentation were clinically suggestive of a fixed drug eruption (FDE). For further diagnosis, the patient was tested intradermally with intravenous preparations of fluconazole, voriconazole and metronidazole on the left volar lower arm, with late readings at 24 and 48 hours. Additional patch tests were performed with the same medications as above, "as is", and itraconazole oral solution soaked on filter paper on the dorsal part of her left upper arm, as well as in terms of a local provocation test on pigmented areas on her left leg. Further patch tests were performed on the upper right arm and in previously lesional (FDE) skin on the right leg with commercially available topical preparations of terbinafine, isoconazole, and ketoconazole. Large Finn Chambers were used.

As all skin tests gave negative results, an oral drug provocation test (DPT) with 150 mg of fluconazole was performed, and induced reappearance of the FDE (Figures 1 and 2) 5 hours later. A skin biopsy from the lesion on the left palm confirmed the diagnosis of FDE (Figure S1). To evaluate possible cross-reactivity with structurally related substances, additional oral DPTs were performed later with 100 mg of itraconazole and 500 mg of the structurally related antibiotic metronidazole; these were well tolerated.

DISCUSSION

Acute FDE lesions can develop within 30 minutes to 8 hours after drug administration.[4,5] Lesions are clinically characterized as single or

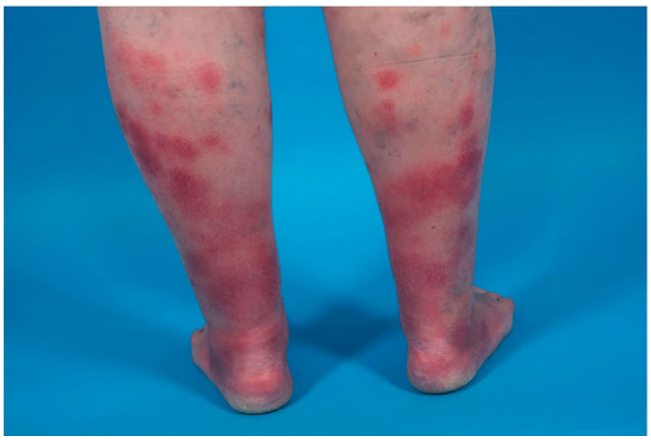

FIGURE 1 Well-circumscribed round erythematous macules and plaques on both lower legs

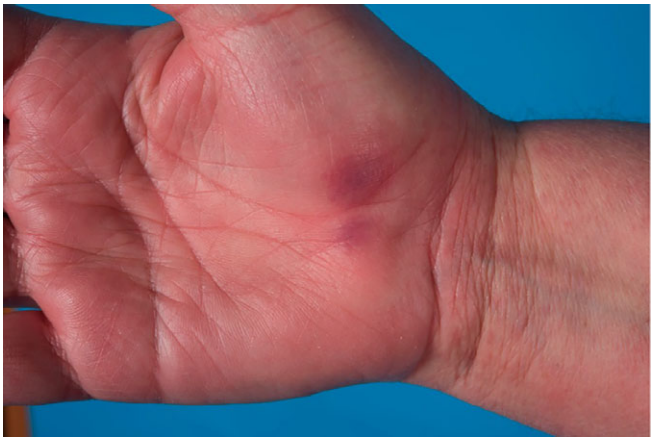

FIGURE 2 Well-circumscribed round erythematous macules and plaques on palms

multiple, sharply demarcated, round or oval erythematous patches or plaques that may become vesicular or bullous.[6] Because of the diversity of clinical pictures, the correct diagnosis may sometimes be difficult to achieve. With repeated exposure, new lesions can appear, and the previous lesions may increase in size.[7] Barbiturates, antibiotics (sulfonamides, tetracyclines, penicillin, and erythromycin) and nonsteroidal anti-inflammatory drugs are common and well-known causative agents. Oral antifungal agents, such as fluconazole, are rarely associated with FDE, and FDE caused by these is often underdiagnosed. Since approval was given to fluconazole in 1989, there have been only 26 case reports published in MEDLINE, which means that we add our case as the 27th case of FDE caused by fluconazole to the medical literature.

Cross-reactivity was previously observed among antifungals, especially within the structurally related triazole group.[8–10] No cross-reactivity was observed in our patient, either to the alternative antifungal itraconazole or to the structurally similar antibiotic metronidazole. Another important point illustrated by our case is the limited sensitivity of skin tests. In cases with negative skin test results, it is essential to perform a DPT in order to confirm or exclude the diagnosis.

In conclusion, our case highlights the importance of, and need for, awareness among medical practitioners that even the often-prescribed and generally well-tolerated fluconazole can, from time to time, cause FDEs. Fluconazole should therefore be added to the list of FDE-inducing drugs.

CONFLICT OF INTEREST

The authors declare no potential conflict of interests.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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