

## CLINICAL REPORT

# A Young Woman with Recurrent Vesicles on the Lower Lip: Fixed Drug Eruption Mimicking Herpes Simplex

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**A 23-year-old woman presented with recurrent herpetiform vesicles of the lower lip, but all diagnostic measures for herpes virus infection including herpes viridae specific PCR were negative. Medical history revealed that she also had chronic recurrent vulvovaginal candidiasis, which had been treated with various regimes, including repetitive applications of fluconazole. Consequently, fluconazole-induced fixed drug eruption was suspected, but skin tests performed with fluconazole remained without response. Consecutive repeated oral provocation tests with fluconazole were carried out and resulted in the development of burning herpetiform vesicles of the lower lip. Histopathology revealed a subepidermal and superficial perivascular infiltrate, basal vacuolated and apoptotic keratinocytes, intra-epidermal lymphocytes and intra-epidermal multilocular vesicles. Together with the clinical history and picture, fluconazole-induced fixed drug eruption mimicking labial herpes simplex virus infection was diagnosed. Oral provocation tests with an alternative systemic antifungal treatment, itraconazole, were well tolerated, systemic therapy with itraconazole was initiated, and no further labial vesicles developed. *Key words: fixed drug eruption; fluconazole; antimycotics; herpes simplex labialis; chronic recurrent vulvovaginal candidiasis.***

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Drug hypersensitivities are considered to be the chameleons of clinical dermatology and may mimic systemic or localized infectious diseases. T-cell mediated delayed type hypersensitivity reactions in response to drugs typically present as different forms of exanthemas and may develop into severe drug reactions. Fixed drug eruption (FDE) is a localized variant of a delayed type hypersensitivity reaction in response to drugs and is characterized by the sudden onset of single or multiple, sharply demarcated, erythematous macules and plaques (1). FDEs are common types of drug eruptions, usually ranking on the second or third place amongst all cutaneous drug-induced

side effects. FDE might present as bullous erythemas, thus mimicking vesiculo-bullous dermatoses (2).

Chronic recurrent vulvovaginal candidiasis (CRVC) is estimated to occur in 5–8% of women during their reproductive years, and successful therapy of CRVC is difficult, often including oral intake of fluconazole or other antimycotics (3). Fluconazole is an effective and safe therapeutic option for CRVC, but may lead to cutaneous adverse effects, as in our patient (4). We report here a patient who presented with herpes-like lesions on the lip, but was eventually diagnosed with a FDE due to treatment with fluconazole for CRVC.

## CASE REPORT

A 23-year-old woman presented with recurrent vesicles at the outer aspects of the lower lip that developed after a few days of burning, itching and stinging, characteristic for recurrent localized herpes simplex. Treatment with acyclovir was not successful. The patient's medical history was unremarkable despite having CRVC for 4 years, which was treated with various topical drugs leading to short-term improvements. Systemic treatment with fluconazole was therefore carried out every 2–4 weeks. No other medication was reported, except for oral contraceptives. The patient experienced two additional episodes with herpes-like vesicles at the lower lip 2 and 3 months after initial presentation and antiviral therapy was again without effect. History now revealed that these herpes-like vesicles developed concomitantly with the fluconazole treatment.

The first episode of blistering occurred after the intake of the 12th tablet of fluconazole, and the second and third episode after the 13th and 14th tablet, which were taken at 4-weeks intervals. Therefore, a FDE to fluconazole was suspected. Skin tests to detect a delayed type hypersensitivity reaction remained negative. As our patient needed CRVC therapy, oral provocation tests were performed. Ten hours after starting oral provocation with an increasing dosage scheme (25, 50, 100, 125 mg fluconazole; cumulative dose 300 mg) a burning and itching erythema developed on both aspects of the lower lip (Fig. 1), developing into herpes-like vesicles within 1 day (Fig. 2) and confluent blisters after 3 days (Fig. 3) – the patient showed exactly the same reaction as reported from earlier episodes. We could neither detect Herpes-type virions by



Fig. 1. Ten hours after starting oral provocation with 25, 50, 100, 125 mg fluconazole (cumulative dose 300 mg) the patient developed a burning and itching erythema on both sides of the lower lip.

electronmicroscopic negative staining nor herpes simplex virus specific RNA by PCR. To establish the diagnosis, a biopsy was taken and histopathology revealed intra-epidermal multilocular vesicles with epidermal immigration of lymphocytes, basal vacuolated and apoptotic keratinocytes, and a superficial perivascular infiltration consisting of lymphocytes and eosinophilic granulocytes around dilated vessels typical for FDE (Fig. 4). To identify a treatment option for CRVC, oral provocation tests were also carried out with itraconazole and remained without skin eruptions. Thus fluconazole-induced FDE mimicking a herpes simplex virus infection was diagnosed based on the patient's history, clinical and histopathological appearance and the provocation test. Itraconazole treatment was recommended, leading to clearance of CRVC without recurrence of labial vesicles.



Fig. 2. One day after oral provocation with fluconazole the patient presented with herpetiform vesiculae on the sites of the pre-existing erythema.

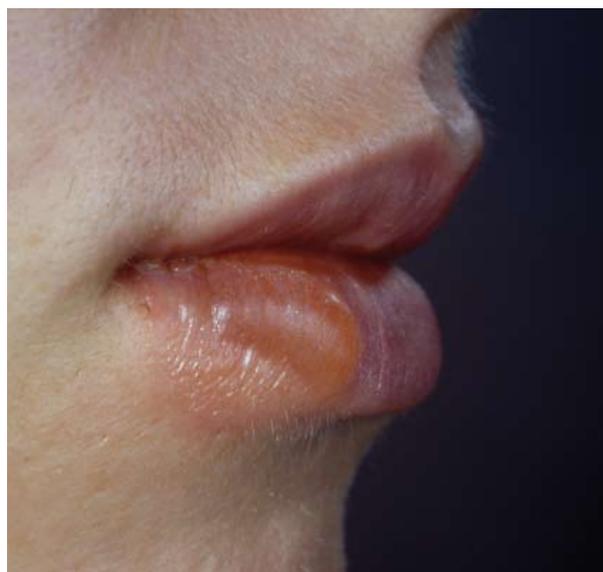


Fig. 3. Three days after the second provocation, the patient developed tense confluent blisters.

## DISCUSSION

We report here on a patient with fluconazole-induced FDE mimicking labial herpes simplex virus infection. FDE was first described by Bourns in 1889, and 5 years later, Brocq termed it “*éruption érythémato-pigmentée fixée*” (5). FDE is characterized by the sudden onset of single or multiple, sharply demarcated, erythematous macules and plaques with or without blistering, often resulting in a residual post-inflammatory pigmentation.

Bullous FDE has been reported as mimicking either localized bullous pemphigoid or herpes simplex labialis (6). The fixed localization of FDE is a diagnostic hallmark. Sites of predilection are the hands, feet, perianal area and, in approximately 50% of cases, the genital and oral mucous membranes (7). In addition to drugs, preservatives or food may also elicit fixed eruption, resulting in a fixed food reaction (8).

When taking a history for FDE, in addition to oral intake, intravenous, sublingual, rectal, bronchial and intradermal application of substances need to be considered (1). Sensitization in FDE may occur a few weeks to several years after starting the medication (1). In our patient fluconazole-induced FDE developed after 6 months of recurrent fluconazole intake. The onset of FDE after drug exposure may vary extensively, with early eruptions documented after 30 min. Only occasionally, FDEs occur with symptoms such as fever, nausea, diarrhoea, abdominal cramps, conjunctivitis, or urethritis (9).

The histopathology of FDE is the result of drug-specific CD8+ T lymphocytes that persist *in loco* and induce apoptosis of basal keratinocytes after activation, leading to oedema, vascular dilatation and a perivascular inflammatory infiltrate dominated by lymphocytes (1).

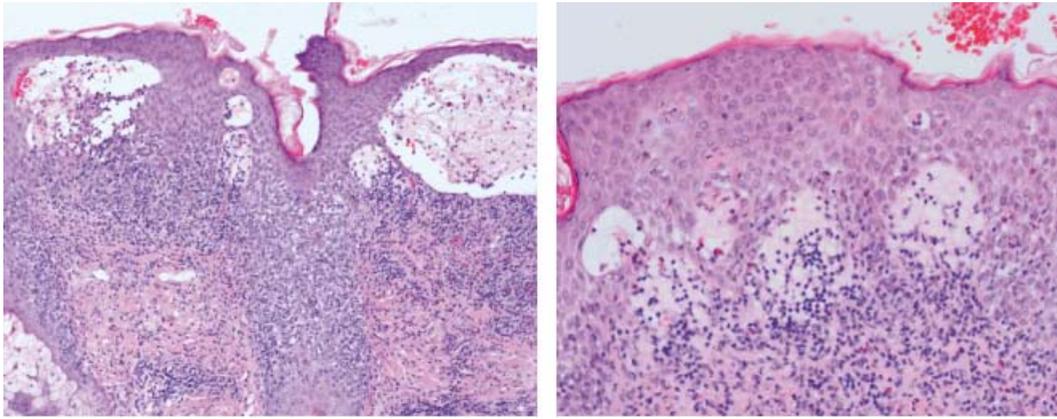


Fig. 4. Histopathology: intra-epidermal multilocular vesiculae with epidermal immigration of lymphocytes, basal vacuolated and apoptotic keratinocytes, and a superficial perivascular infiltration consisting of lymphocytes and eosinophilic granulocytes around dilated vessels (haematoxylin-eosin stain, original magnification: left-hand photograph  $\times 2.5$ , right-hand photograph  $\times 25$ ).

As in our patient, vast apoptosis of keratinocytes might lead to intra-epidermal blistering. In contrast, herpes virus infection shows accumulation of viral inclusion bodies, homogenous ground-glass appearance of the epidermis, multinucleated keratinocytes and intra-epidermal vesiculation due to ballooning degeneration of the keratinocytes.

For confirmation of FDE, skin and provocation tests are carried out (1, 10), with some patients responding to intralesional skin tests. However, patients with negative skin tests may respond with FDE after systemic provocation, as in our patient, and as has already been reported for fluconazole (7, 11).

The current concept of the underlying mechanisms of FDE focuses on persistent dermal or intra-epidermal CD8<sup>+</sup> T lymphocytes. These cells are characterized by the surface pattern of effector-type or effector-memory T cells (expression of CD45RA, CD11a, CD11b, CLA,  $\alpha_E\beta_7$  and absence of CD27, CD28, CD56, CD62L). Furthermore, these T cells express the early activation marker CD69 even before challenge, and thus seem to persist in a state of activation. After challenge, these cells undergo phenotypic conversion from CD45RA<sup>+</sup> to CD45RO<sup>+</sup> memory-type T cells and produce large amounts of cytokines, particularly IFN- $\gamma$ . Along with their cytolytic activity, this induces apoptosis of keratinocytes and the clinical picture of erythema, eczema-like lesions or even blistering (12).

In a series of cutaneous drug reactions recorded between 1956 and 1990, FDE accounted for 16% of all reactions (13); however, the frequency of FDE induced by a specific drug depends on the frequency of prescription and the potential of that drug to induce FDE. In fact, barbiturates used to be the most common drugs inducing FDE; however, according to a more recent study antibiotics (tetracyclines, penicillin, aminopenicillins, trimethoprim, erythromycin, rifampicin, fluoroquinolones) most often induce FDE, followed by NSAID's (aspirin, mefenamic acids, naproxen, ibuprofen) (14). These data

are due to a decreased use of barbiturates and an increase in the intake of the latter medications in the population.

Until now 7 cases of fluconazole-induced FDEs have been published. In 1994 Morgan & Carmichael (15) first described a 27-year-old man with an 18-month history of a recurrent rash (15 episodes) on the extensor surfaces of his elbows. Since then other reports on fluconazole-induced FDE followed, most of them being multilocular, as in a 36-year-old woman with FDE that included blistering in the mouth (16, 17) and 2 other reports demonstrating involvement of the lips (12, 18). Importantly, FDE has also been reported for ketoconazole, terbinafine and griseofulvin (19–21), but not for other imidazole derivatives e.g. clotrimazole and miconazole or triazole derivatives such as itraconazole, voriconazole, and posaconazole.

Treatment of chronic recurrent vulvovaginal candidiasis includes the prophylactic use of antimycotics. In general, fluconazole is a safe oral antifungal agent with a favourable spectrum and few side-effects (4). A single tablet of 150 mg fluconazole administered once weekly is recommended for CRVC, resulting in clearance in 90.8% of the patients after the initial 6 months (22). However, long-term therapy with weekly fluconazole may be ineffective and lead to sensitizations and allergic reactions, as seen in our patient.

In patients with recurrent infections and repeated antimicrobial treatments, especially, new localized skin lesions should be considered as potentially drug-induced, as in our patient with fluconazole-induced herpes-like FDE of the lips.

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