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**Case Report**

# Fixed drug eruption by fluconazole: A case report

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**Abstract** A common kind of cutaneous adverse medication reaction is fixed drug eruption (FDE). There are many groups of drugs that are notorious culprits. Fluconazole is a very commonly prescribed anti-fungal agent in dermatology outpatient departments, and up till now, less than 30 cases have been reported where Fluconazole was an established causative agent of the FDE. We report a case of FDE caused by Fluconazole which has not ever been established in our dermatology outpatient department prior to this (with an influx of about 1000 patients every day). The lack of clinical suspicion of the association of FDE with fluconazole might be the reason for under diagnosis. A follow-up patient of SLE presented to us with oral candidiasis for which she was prescribed oral fluconazole. A week later, she came back to the OPD with complaints of FDE-like lesions involving her trunk and proximal extremities associated with burning pain. She admitted to having experienced such episodes twice before this time, but they were of much less severity and subsided on their own within a few days. The intermitted nature of the flares upon drug intake and the morphology of her skin lesions rose our clinical suspicion of FDE. While dealing with cases of FDE, dermatologists should keep in their mind to identify causes other than the well-established and notorious culprits. This will help in making the correct association and diagnosis and will be beneficial to avoid more severe flares subsequently.

***Key words***
Fixed drug eruption; Fluconazole.

## Introduction

Cutaneous fixed drug eruption is a distinctive adverse drug allergy attributed to a drug in the form of either a well-defined erythematous patch, or plaque, or can be a bullous eruption. It occurs in the form of recurrent lesions at the same site after re-exposure to the culprit agent.[1,2] It usually heals with residual hyperpigmentation which remains for months and years and can be used for site recognition of fixed drug eruption.[3] Most common drugs implicated are antimicrobials and anti-inflammatory agents, with an increased risk of extensive and multiple lesions in patients with a history of FDE with the concurrent intake of several drugs due to comorbid conditions. There are multiple variants of FDE and we report a generalized non-bullous FDE variant caused by an uncommon but very commonly prescribed during in the dermatology OPD, characterized by well-defined erythematous to violaceous round or oval plaque.[4]

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## Case report

A 35-year-old female was diagnosed with systemic lupus erythematosus four years prior to this study and was currently on daily maintenance oral prednisolone 5mg and Hydroquinone 400mg. The patient did not have any active disease symptoms in past 6 months. Now, she presented to us with the complaint of oral mucosal involvement. There was a strong clinical suspicion of oral candidiasis which was confirmed by a positive candidal smear, for which we prescribed topical antifungal agents

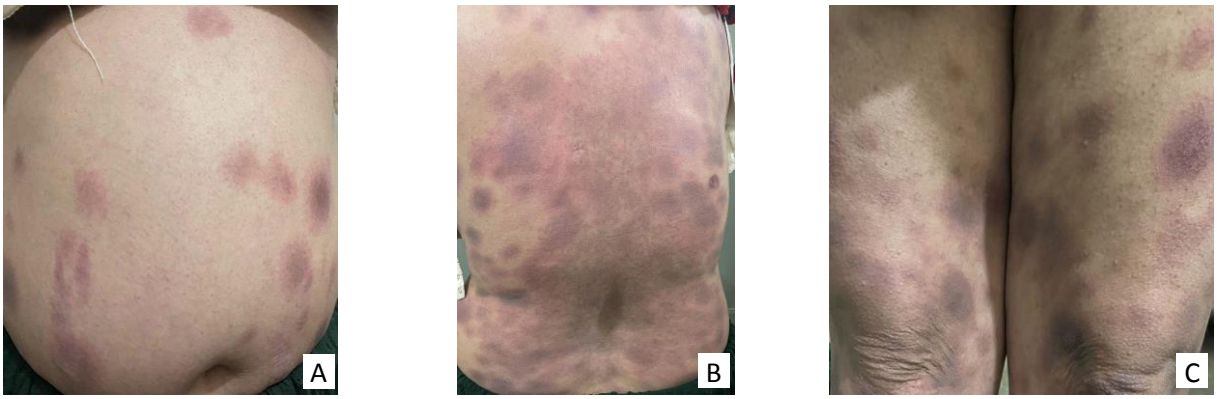


**Figure 1** Generalized non-bullous FDE lesions A) A Dusky, well-demarcated erythematous patches of variable sizes on the abdomen; B) Gross involvement of the back with hyperpigmented patches which are confluent in certain areas; C) Hyperpigmented annular patches of variable sizes present on both lower limbs symmetrically.

with a follow-up visit scheduled two weeks later. On the follow-up visit, the patient still had oral candidiasis, so we added oral fluconazole 150mg once daily to her current therapy while continuing topical antifungal agents.

The patient presented to in the OPD one week later with a complaint of a rash on the body which developed within two days of drug intake. On cutaneous examination, well-defined, round erythematous and edematous plaques of different sizes were present over the abdomen, back, upper limbs, and lower limbs with associated burning and itching. The largest was over the back. There was no involvement of oral, conjunctival, nasal, or genital mucosa. Complete blood count showed increased leukocytes and other laboratory values were within the normal range. SLE symptoms were under control, and anti-dsDNA titers were low, indicating low disease activity, excluding lupus erythematosus-like lesions. We were able to rule out pemphigus vulgaris and Stevens-Johnson syndrome because there was no mucosal involvement. The causality assessment was carried out on the WHO-UMC causality assessment scale. A diagnosis of FDE to fluconazole was made and the patient was asked to stop taking the offending agent. Oral antihistamines and topical steroids were prescribed. This resulted in complete recovery, with only a few residual, hyperpigmented lesions on her follow-up visit one week later.

## Discussion

FDE to fluconazole is very rarely reported, with less than 30 cases reported to date.[5] One of the most often prescribed medications in dermatology is fluconazole. It is a triazole that inhibits the conversion of lanosterol to ergosterol by interfering with lanosterol 14-demethylase. The serious side effects that are most frequently mentioned are biliary hepatitis, nausea, headaches, and vomiting but skin rash is the most frequent cutaneous side effect. Moreover, there have been reports of severe cutaneous reactions including erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, and acute generalized exanthematous pustulosis.

**Figure 2** Erythematous malar rash on cheeks.

**Figure 3** White patches on the tongue indicating oral candidiasis.

FDE is thought to be a lymphocyte CD8-mediated reaction, and the offending substance may cause local reactivation of memory T cell lymphocytes that were initially targeted by the viral infection and localised in epidermal and dermal tissues.[6] Intraepidermal CD8+ T cells appear to be crucial in FDEs. In recovered FDE lesions, these cells stay dormant in a primed state. Upon activation, the primed CD8+ T cells release interferon-gamma and cytotoxic granules such as granzyme B when a causal medication or a structurally related one is administered again. There is further recruitment of cell adhesion molecules on the neighboring keratinocytes, mast cells also assist in the activation of intraepidermal T cells.[7] The recruitment of CD4+ T cells, CD8+ T cells, and neutrophils may be mediated by cytokines and/or adhesion molecules. Histologically, FDE shows pronounced pigmentary incontinence and basal cell hydropic degeneration. The epidermis shows scattered keratinocyte necrosis with eosinophilic cytoplasm and pyknotic nuclei (Civatte bodies), whereas the upper dermis shows edema as well as perivascular lymphocytic infiltrate along with eosinophils. Lesions in the healing phase can be characterized by the presence of pigment-laden macrophages in the upper dermis.[8]

FDE can affect both men and women equally, although a study found that the majority of patients were females in their third decade of life.[9] A few studies have also shown that males are more likely to be affected than females, but there is no gender preponderance in FDE.

The differentials were ruled out on the basis of careful history and examination considering the site, number of lesions, and stage of evolution. SLE symptoms were in control and anti-dsDNA titers were low showing low disease activity to rule out lupus erythematosus type of lesions. The absence of mucosal involvement helped us in ruling out pemphigus vulgaris, and Stevens-Johnson syndrome (SJS).

The most frequently affected sites in our case were the extremities (50.4%), followed by the trunk and back.[10] Our patient has disseminated FDE involving multiple sites. It has been reported that many cases of generalized fixed drug eruption (GFDE) other than bullous GFDE are first presented as FDE on limited body sites only but later on with repeated drug exposure can lead to a more disseminated form of disseminated FDE by repeated exposure to the causative drug.

Clinically, the high proportion of patients with FDEs highlights the significance of identifying an FDE and avoiding giving a patient who has previously experienced an FDE the same medicine or one that is structurally similar to it. Patients with GFDE usually take multiple drugs at a time,[7] which is consistent with the results of one study we encountered. Moreover, the prescriber frequently isn't aware of the current medication regimen because a patient could go to various medical centers and doctors and this is thought to be one of the issues that make it difficult to identify the causative drug. Our patient reported two previous self-resolving flares with much less severity with some unknown drug, she was unable to recall or provide any medical record and had no knowledge of drug allergies, but she was taking multiple drugs for her autoimmune condition which might contribute to the eruption. Therefore, physician and patient education are both required to avoid any unintended re-exposure to a causative drug that can be more severe subsequently. Concurrent use of several medications, the absence of a specialized clinical examination, and other factors might contribute to the difficulty in pinpointing a single causative agent.

Therefore, this case is being reported both for its rarity and to increase awareness of the numerous

side effects associated with this widely used medication.

To avoid any side effects associated with this widely prescribed medication, we advise general practitioners to increase their knowledge of FDE and uncommon associations to avoid misdiagnosis.

## Conclusion

FDE to fluconazole is rare. Fluconazole is a commonly prescribed drug in dermatology outdoor facilities, to treat fungal infections, however, while prescribing its association to cause FDE is usually not considered, and previous drug reaction history is not elicited. Dermatologists should do a thorough history, and clinical examination, and rule out any previous history of allergies while prescribing fluconazole. Healthcare providers should have a high level of suspicion and be aware of the likelihood of cutaneous adverse reactions to prescribed drugs.

***Patient perspective*** Patient had two mild, self-resolving episodes of drug-related skin lesions in the past with an inadequate diagnosis and inability to establish the association and adequate patient education. Being a known case of dermatological disease, it was generally simpler for the practitioner as well as the patient to blame SLE for every new lesion. It was very satisfying for the patient to be correctly addressed and educated about her drug allergy.

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