

## BRIEF ARTICLE

## Non-Pigmenting Fixed Drug Eruption Due to Fluconazole Without Cross-Reactivity to Itraconazole

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### ABSTRACT

Fixed drug eruption is an uncommon cutaneous skin reaction that is most frequently attributed to antibiotics, non-steroidal anti-inflammatories, and paracetamol. Localized hyperpigmentation often results after the resolution of acute inflammation. Rarely, do fixed drug eruptions resolve without hyperpigmentation. Non-pigmenting fixed drug eruption (NPFDE) is an uncommon subtype that is characterized by well-demarcated, tender erythematous plaques that resolve without post-inflammatory hyperpigmentation. NPFDE has most frequently been associated with pseudoephedrine and piroxicam, but we report a case of a 48-year-old female with repeated occurrences of fluconazole-induced non-pigmenting fixed drug eruption. Clinical diagnosis of non-pigmenting fixed drug eruption was made based on the correlation of the lesion appearing within 2 hours after fluconazole ingestion, and previous history of similar reactions after fluconazole intake with resolution without residual pigmentation.

### INTRODUCTION

Fixed Drug Eruption (FDE) is a well-circumscribed, erythematous plaque that recurs as one or few lesions on the skin or mucous membranes always in a fixed location upon ingestion of a drug.<sup>1</sup> Acute FDE usually presents a single or small number of dusky red or violaceous plaques that resolve, leaving post-inflammatory hyperpigmentation. The most commonly implicated drugs are analgesics (non-steroidal anti-inflammatories and paracetamol) and antibiotics.<sup>2</sup> A less common variant is a non-pigmenting fixed drug eruption (NPFDE) which is characterized by a well-circumscribed, tender

erythematous plaques that fade without pigmentation over 2-3 weeks.<sup>3</sup> Antifungal agents are rarely associated with NPFDE. Here we report a case of a 48-year-old female with repeated occurrences of fluconazole-induced non-pigmenting fixed drug eruption.

### CASE REPORT

A 48-year-old Caucasian woman presented with a recurrent, pruritic, painful, cutaneous lesion on the left lateral 3<sup>rd</sup> phalanx. The physical exam showed a single, 2mm erythematous macule that presented after treatment of esophageal candidiasis with 400mg of fluconazole. The initial presentation

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**Figure 1.** A. 60 min after ingestion of fluconazole. B. Drug eruption becomes visible. C. and D. Drug eruption progression Day 1.



**Figure 2.** A. Drug eruption day 3. B. Progressive improvement of drug eruption day 4. C. Continued resolution without hyperpigmentation by day 7. D. 2 months after drug eruption to fluconazole during the trial with itraconazole.

was a stinging sensation in the area 60 minutes after ingestion, and the lesion presented 2 hours after ingestion of fluconazole and progressively darkened throughout the day (**Figure 1**).

The patient denied concurrent use of other medications during this episode. She was treated symptomatically with antihistamines and topical 0.1% triamcinolone cream. The drug eruption resolved after one week. (**Figure 2**).

She had a history of similar lesions in the same location, each after taking fluconazole. Each episode recurred in the same location and lasted approximately one week resolving without residual pigmentation. Previous episodes occurred in 2013 and 2018 which were initially diagnosed as spider bites. It wasn't until this recent episode that the patient remembered that she had been taking 150 mg of fluconazole for vaginal candidiasis before each of the previous episodes. Prior to the first episode in 2013, the patient had been taking azithromycin for an upper respiratory infection which caused the vaginal

candidiasis requiring fluconazole. Antibacterial agents are commonly known to cause FDE, but since 2013 the patient has taken azithromycin on multiple occasions without a problem making it unlikely to be the culprit. The patient did not consent to an oral rechallenge.

Clinical diagnosis of NPFDE was made based on the correlation of the lesion appearing after drug ingestion, and previous history of similar reactions after fluconazole intake with resolution without residual pigmentation. She was advised to avoid fluconazole, but due to an incomplete treatment course for esophageal candidiasis, she was given itraconazole 100mg twice a day (BID) for 14 days. She tolerated the treatment well and reported no symptoms of pain, pruritis, or recurrent drug eruption (Figure 2D).

## DISCUSSION

FDE is a common cutaneous adverse drug reaction that occurs after ingestion of a causative agent. Previously, FDEs were assumed to be a less common form of drug eruption, but a recent study shows that they make up 49.2% of reported cases in certain geographic areas.<sup>4</sup> FDEs classically present as circular, well-demarcated erythematous-violaceous plaques occurring on the skin or mucous membranes that recur in a fixed location upon reingestion of a drug leaving residual hyperpigmentation.<sup>1</sup> FDEs can be morphologically categorized into clinical subgroups. These clinical variants include Erythema multiforme-like fixed drug eruption, generalized fixed drug eruption, generalized bullous fixed drug eruption, and non-pigmenting fixed drug eruption.

FDEs can be caused by the administration of any drug, but frequent offenders often

change based on prescribing trends. One of the emerging culprits that have shown to be a trigger in over 30 case reports is fluconazole, however, the non-pigmenting variant has not been commonly reported.<sup>2</sup> NPFDE is a rare subtype that is characterized by well-demarcated, tender erythematous plaques that resolve without post-inflammatory hyperpigmentation.<sup>5</sup> NPFDE has most frequently been associated with pseudoephedrine and piroxicam.<sup>5,6</sup> Lesions from FDE usually occur 30 min to 8 hours after drug ingestion and resolve after discontinuation of the offending agent. After the initial acute reaction, post-inflammatory hyperpigmentation develops and often intensifies with following episodes. However, in our patient, the painful, pruritic, erythematous lesion developed approximately 2 hours after ingestion and resolved without residual hyperpigmentation in approximately one week after each episode.

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