

CASE REPORT

Fluconazole Induced Fixed Drug Eruption

Chi Yeon Kim, M.D., Jin Gu Kim, M.D., Chee Won Oh, M.D.¹

Department of Dermatology, School of Medicine, Gyeongsang National University & Gyeongsang Institute of Health Science, Jinju,
¹Kangwon National University Hospital, Chuncheon, Korea

We report on a rare case of fluconazole induced fixed drug eruption in a 62-year old female patient. She was referred to our department for multiple erythematous itchy maculopatches on the face, neck, both upper arms, and trunk area, which had occurred over the previous 6 months. Her attending physician prescribed fluconazole for treatment of onychomycosis. Patch test and oral provocation were performed. The patch test showed a negative result; however, the result for oral provocation was positive, confirming this as a rare case of fluconazole induced fixed drug eruption. To the best of our knowledge, this is the first reported case in Korean dermatologic literature. (*Ann Dermatol* 23(S1) S1~S3, 2011)

-Keywords-

Drug eruption, Fluconazole

INTRODUCTION

Fixed drug eruption (FDE) is a distinctive variant of drug induced dermatoses with a characteristic recurrence at the same sites of the skin or mucous membrane after repeated administration of the causative drug¹. FDE is characterized by the onset of single or multiple, sharply demarcated, erythematous macules and plaques with or without blistering, often resulting in residual post-inflammatory pigmen-

tation². The hands, feet, genitalia, and perianal areas are the most favored sites³. Drugs most frequently implicated in fixed drug eruption are antibiotics (trimethoprim-sulfamethoxazole, tetracycline, penicillin, and erythromycin), followed by NSAID's (aspirin, mefenamic acids, naproxen, and ibuprofen)². Fluconazole is used for treatment of fungal infection and is known to be relatively safe^{3,4}. Herein we report on a rare case of fluconazole induced fixed drug eruption showing a positive response in an oral provocation test in a 62-year old woman.

CASE REPORT

A healthy 62-year old woman was administered a single 150 mg dose of fluconazole for treatment onychomycosis. Within 3 hours, she noticed multiple pruritic, oval, swollen, erythematous, bright red or dusky red patches measuring 3 to 4 cm with erythematous halos over her face, neck, both upper arms, and trunk (Fig. 1). On further inquiry, she recalled a history of a similar episode about 6 months ago, when she had taken fluconazole for treatment of onychomycosis. The patient had no previous history of any medical conditions, such as allergy or atopic dermatitis. She was not taking any regular medications. In the laboratory study, except for white blood cell count (11,020 cells/mm³, normal 3,600~10,200 cells/mm³), results of blood sugar, liver function test, and urine analysis, Ig E PRIST were all within normal limits. A clinical diagnosis of FDE caused by fluconazole was made. A skin biopsy was performed on an erythematous to brownish patch on her left upper arm. Histopathological findings revealed an appearance of a fixed drug eruption; an interfacial dermatitis with dyskeratotic keratinocytes in epidermis, lichenoid lymphocytic infiltration and pigmentary incontinence in upper dermis (Fig. 2). She was treated with oral prednisolone 10 mg daily for 3 days and 7.5 mg daily for 3 days. Oral antihistamine and topical corticosteroid ointment were also prescribed. The skin lesion re-

Received December 28, 2009, Revised April 4, 2010, Accepted for publication April 6, 2010

Corresponding author: Chee Won Oh, M.D., Department of Dermatology, Kangwon National University, 17-1 Hyoja-dong, Chuncheon 200-722, Korea. Tel: 82-33-258-2188, Fax: 82-33-258-2146, E-mail: deroh@kangwon.ac.kr

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

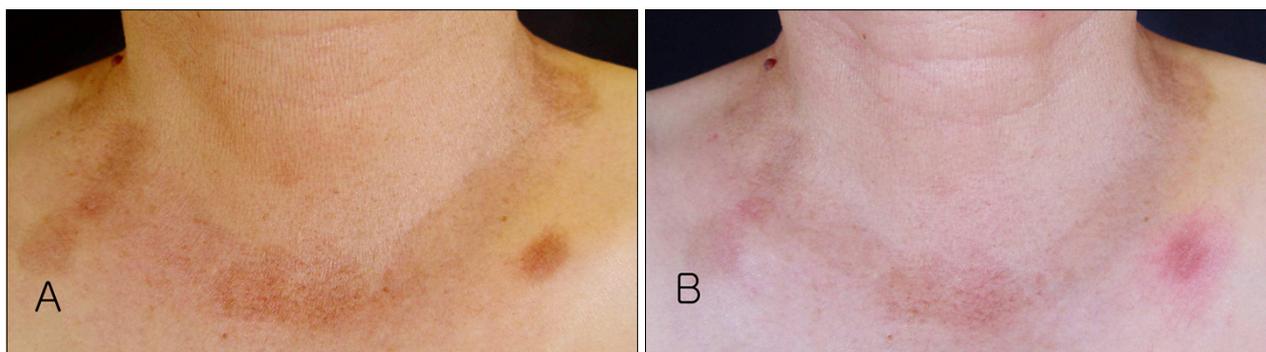


Fig. 1. Oval, swollen, brownish pigmented patches on the ant. Chest (A: Day 3 of eruption, B: 30 minutes after oral provocation).

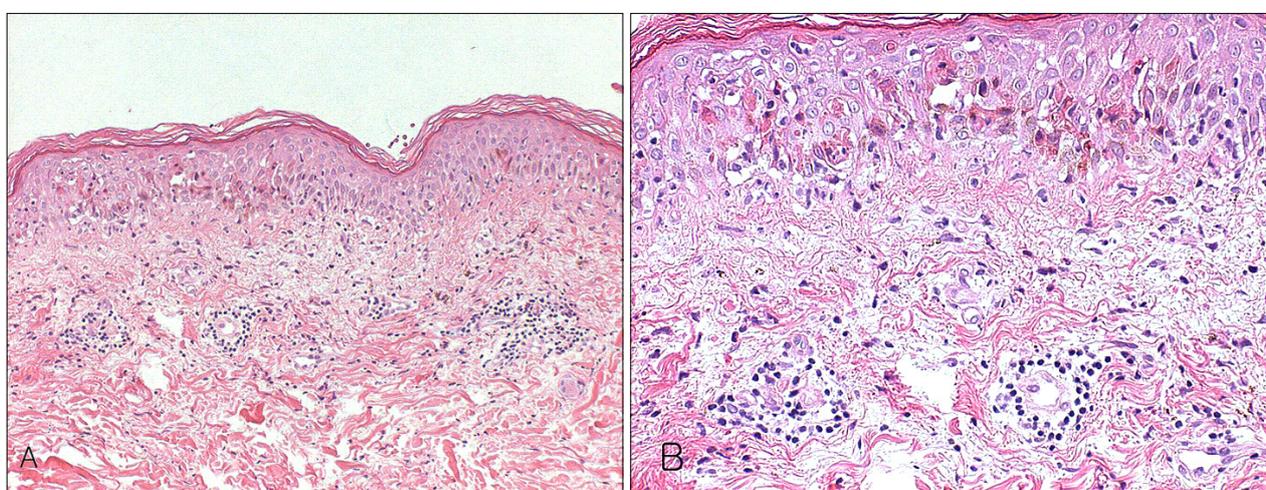


Fig. 2. (A) Skin biopsy specimen shows basal vacuolated and necrotic keratinocytes with dermal inflammatory cell infiltration and pigmentary incontinence (H&E, $\times 100$). (B) Necrotic keratinocytes and basal vacuolation are observed and dermal inflammatory cells are dominant mononuclear cells (H&E, $\times 200$).

gressed after 10 days; therefore, we performed a patch test and an oral challenge test to confirm the relationship between suspected drug intake and drug interaction 4 weeks later. A patch test with fluconazole 0.1%, 1%, and 10% in petrolatum placed on the small Finn chamber was performed on the previous lesion of the anterior chest; results at 48, 72, and 96 hr were all negative. In an oral challenge test with 50 mg fluconazole (one-third of the therapeutic dose), a lesion reappeared with greater rapidity and aggression than before at the same sites after 30 minutes (Fig. 1B). Herein, we report on a rare case of fluconazole induced FDE diagnosed by an oral challenge test and propose addition of fluconazole to the list of drugs that can induce fixed drug eruption.

DISCUSSION

FDE is a distinctive variant of drug induced dermatoses with a characteristic recurrence at the same sites of the

skin or mucous membrane after repeated administration of the causative drug¹. It was first described by Bourns in 1889, and, 5 years later, it was termed by Brocq as "eruption erythemato-pigmentee fixe"². Onset of FDE after drug exposure may vary, from 30 min to 8 to 16 hours. On occasion, FDEs may occur with symptoms such as fever, nausea, diarrhea, abdominal cramps, or conjunctivitis^{2,4}. Sites of predilection are the hands, feet, perianal area and, in approximately 50% of cases, genital and oral mucous membranes². Size and number of lesions were found to be greater with recurrence, than with the first attack^{5,6}.

Histologically, acute fixed drug eruption is characterized by marked basal cell hydropic degeneration, with lymphocyte tagging along the epidermodermal junction and individual keratinocyte necrosis. In more advanced lesions, subepidermal vesiculation may be a feature^{6,7}. Infiltration of lymphocytes, histiocytes, and neutrophil polymorphs is evident in the upper dermis, and eosinophils may some-

times be prominent^{6,7}. In our case, the histologic examination revealed a lichenoid infiltrate, basal cell vacuolization, and a superficial perivascular lymphocytic infiltrate consistent with FDE.

FDE can be caused by many different drugs; however, the most frequently implicated medication appears to be antibiotics followed by NSAID's. In our case, there was no previous history of allergy, atopic dermatitis, or any medications other than fluconazole. To the best of our knowledge, regarding antifungal agents, the literature mentions only seven cases of FDE caused by fluconazole; one case from the use of ketoconazole, and none caused by itraconazole^{2,3,5}. In Korean dermatologic literature, there have been no reported cases of fluconazole induced fixed drug eruption.

To confirm the diagnosis of FDE, various skin tests, including prick, intradermal, patch, and oral challenge tests using suspected drugs can be performed^{6,8}. In our case, we performed a patch test and an oral challenge test. Respectively, the result of the prick test for FDE may be positive in 24% and intradermal skin tests in 67%⁹. Patch test at the site of a previous lesion was positive in up to 43%⁹. For FDE, sensitivity of skin provocation test is variable. If positive results are useful, negative results are not an indication that the drug is not a causative agent³. If necessary, an oral provocation test may be performed^{3,8}. In a reported case of fluconazole induced FDE, skin provocation tests were performed with a preparation of fluconazole 1%, 10% (a dilution of fluconazole parenteral solution in saline or fluconazole in petrolatum¹⁰) and oral provocation tests were performed with 25 mg, 50 mg, and 150 mg². Our patient underwent a patch test and an oral challenge test for confirmation 4 weeks later. Patch test with fluconazole 0.1%, 1%, and 10% in petrolatum on the previous lesion showed only negative results. Otherwise, in an oral challenge test with 50 mg fluconazole (one-third of the therapeutic dose), a lesion was provoked with greater rapidity and aggression after 30 minutes.

Fluconazole is used for treatment of fungal infection and is known to be relatively safe^{3,4}. Commonly observed adverse effects due to fluconazole include nausea, vomiting,

and elevated liver enzyme level. Anaphylactic reaction, generalized exanthematous pustulosis, maculopapular rash, and FDE have been rarely reported in the literature^{2-4,10}. Although occurrence of fluconazole induced FDE is rare, once FDE is induced by fluconazole, the size and the number of skin lesions tend to be greater with recurrence than with the first attack. Patch test sensitivity is not 100% and false negative results can occur, so that results of the provocative skin test may not match the clinical manifestation. In conclusion, it should be kept in mind that use of fluconazole can result in development of fixed drug eruption and fluconazole should be prescribed carefully.

REFERENCES

1. Kim YS, Kang HJ, Hahm JH. A case of generalized fixed drug eruption due to mefenamic acid. *Ann Dermatol* 1996;8:211-214.
2. Benedix F, Schilling M, Schaller M, Röcken M, Biedermann T. A young woman with recurrent vesicles on the lower lip: fixed drug eruption mimicking herpes simplex. *Acta Derm Venereol* 2008;88:491-494.
3. Goel A, Jain C. Fluconazole induced fixed drug eruption. *J Dermatol* 2004;31:345-346.
4. Heikkilä H, Timonen K, Stubb S. Fixed drug eruption due to fluconazole. *J Am Acad Dermatol* 2000;42:883-884.
5. Gupta R, Thami GP. Fixed drug eruption caused by itraconazole: Reactivity and cross reactivity. *J Am Acad Dermatol* 2008;58:521-522.
6. Ryou JH, Kim JH, Lee MH. A clinicopathological study of fixed drug eruption. *Korean J Dermatol* 1998;36:30-36.
7. McKee PH, Calonje E, Granter SR. Fixed drug eruption. In: McKee PH, Calonje E, Granter SR, editors. *Pathology of the skin*. 3rd ed. Philadelphia: Elsevier Mosby, 2005:636-638.
8. Kim KJ, Jeong MC, Yoo JH. Clinical study and skin tests of patients with drug eruption. *Korean J Dermatol* 1998;36:887-896.
9. Barbaud A, Reichert-Penetrat S, Tréchet P, Jacquin-Petit MA, Ehlinger A, Noirez V, et al. The use of skin testing in the investigation of cutaneous adverse drug reactions. *Br J Dermatol* 1998;139:49-58.
10. Di Leo E, Nettis E, Priore MG, Ferrannini A, Vacca A. Maculopapular rash due to fluconazole. *Clin Exp Dermatol* 2009;34:404.