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Fluconazole-Induced Fixed Drug Eruptions

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ABSTRACT: Fungal infections, although less common than bacterial and viral infections, present significant health risks, particularly in immunocompromised populations. Azole antifungals, such as fluconazole, are primary treatments for various fungal infections due to their efficacy and broad spectrum of action. However, adverse drug reactions (ADRs) associated with fluconazole can complicate treatment protocols. We report the case of a 44-year-old female with a medical history of type II diabetes mellitus, hypothyroidism, and a previous episode of Stevens-Johnson Syndrome (SJS) in 2017. She developed severe cutaneous reactions characterized by itching, eruptions, and blackish discoloration over multiple body areas, alongside systemic symptoms such as flank pain and breathing difficulties. These symptoms emerged following the administration of fluconazole for a vaginal infection. The clinical diagnosis leaned towards urticaria potentially linked to fluconazole intake, given her improvement upon drug discontinuation. Laboratory findings were notable for elevated inflammatory markers and dysregulated glucose levels. The patient's management included cessation of fluconazole, initiation of symptomatic treatments including antihistamines and corticosteroids, and temporary switching to insulin from oral hypoglycemic agents. This case illustrates the complexity of managing patients with a history of severe drug reactions. It highlights the challenges in distinguishing between drug-induced urticaria and manifestations related to previous adverse reactions such as SJS. A causality assessment suggested a possible relationship between the patient's symptoms and fluconazole administration. Vigilance for ADRs in patients with complex medical histories is crucial, especially when prescribing medications known for severe potential side effects. Early recognition and intervention are key in preventing the escalation of adverse outcomes in susceptible individuals. Further studies are needed to explore safer therapeutic alternatives for such high-risk patients.

KEYWORDS: Fluconazole, Steven-Jhonson-Syndrome, Urticaria, Fixed Drug Eruptions, Case Report

I. INTRODUCTION:

While bacterial and viral infections are more common than fungal infections, throughout the past 25 years, there has been a notable increase in the frequency of fungal infections in humans. To effectively treat localized and generalized candidiasis, cryptococcosis, histoplasmosis, pulmonary and systemic aspergillosis, dermatophytes, coccidioidomycosis, blastomycosis, penicilliosis, sporotrichosis, and mucormycosis, azole antifungal agents are the most abundant and effective class of synthetic antimycotics (1).Because they are more difficult to identify and more likely to develop chronic, and potentially fatal, systemic fungal infections are considered more dangerous. Despite the significant danger of causing antibiotic resistance, prophylactic therapy is occasionally recommended for individuals with HIV and those undergoing bone marrow transplants. Triazoles remain the most appropriate and manageable medication for patients to take at home, even if new antifungals become available. They are the first-line treatment for systemic fungal infections. There are currently roughly 20 azole antifungal chemotherapy products on the market, however the majority of these are primarily intended for topical application. They are divided into two categories:azoles having three nitrogen atoms in the azole ring (the triazoles, of which fluconazole is the most representative of the class, followed by itraconazole, posaconazole, voriconazole, and more recently isavuconazole). Azoles with two nitrogen atoms in the azole ring (the imidazoles, including clotrimazole, econazole,

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ketoconazole, miconazole, and tioconazole). Fluconazole is frequently used to treat infections brought on by dermatophytes or yeasts (2).One common bis-triazole antifungal drug is fluconazole. It primarily works by blocking the activity of cytochrome P45014a-demethylase (P45014DM), which stops lanosterol from being converted to ergosterol in the sterol biosynthesis pathway. When it comes to fungi, fluconazole appears to be more selective than human P-450 enzymes (3). In addition to treating vaginal, oropharyngeal, and esophageal candidiasis, it also prevents fungal infections in immunocompromised patients and treats cryptococcal meningitis. Fluconazole has been shown in certain research to be useful in the treatment of systemic Candida infections, such as pneumonia, disseminated candidiasis, and candidemia, as well as urinary tract infections (4). The body generally responds well to fluconazole. However, side effects like nausea, vomiting, and elevated liver function tests are frequently reported. Headaches, vertigo, diarrhea, heartburn, stomach discomfort, altered taste perception, upset stomach, severe exhaustion, decreased appetite, upper quadrant pain, jaundice, dark urine, pale feces, flu-like symptoms, and seizures are less frequent adverse effects. Anaphylactic reactions, angioedema and facial edema, pruritus, urticaria, erythematous or maculopapular rash, and exfoliative skin reactions, such as toxic epidermal necrolysis and Stevens-Johnson Syndrome (SJS), are examples of hypersensitivity reactions that have been observed (5). The most typical adverse effects of fluconazole include rashes on the skin, headaches, nausea, abdominal pain,and acute exanthematous pustulosis throughout the body(2). There have also been reports of Stevens-Johnson syndrome and multiple instances of fixed drug eruption (6–9). An inflammatory condition called urticaria can cause momentary wheals, angioedema, or both, but it doesn't cause systemic symptoms. It is the result of mast cell degranulation, which can occur naturally or be brought on by a variety of substances. For less than six weeks, acute urticaria is frequently linked to food or medication consumption, infections, or both. The primary clinical manifestation of urticaria is wheals, which are round or polycyclic in shape, vary in size, and are marked by edema and fluctuating erythema. They usually have an uneven distribution, are itchy, and go away in less than a day without any complications. Angioedema is a painful edema that goes away in less than 72 hours, usually affecting the deep dermis or subcutaneous tissues. The superficial dermis swells in CU histology, accompanied by vascular dilating withoutleukocytoclasia or wall destruction. While there isa noticeable perivascular eosinophilic and neutrophilic infiltration, macrophages and lymphocytes are not as prevalent (10). The differential diagnosis points towards urticaria, fixed drug eruptions and erythema multiforme. They can be distinguished by the clinical features. Urticaria is presented as wheels for <24 hours and aginoedema. Fixed drug eruptions are presented as red/pruple coloured, well demarcated round or oval patches. Erythema multiforme is presented as pink/red papules which develops in plaques and can further be seen as classic target lesions (10).

Every time a drug is administered, one or more skin lesions at the same location develop. This condition is known as fixed drug eruption (FDE). After each exposure, sites may grow in quantity and size. Lesions are often well-defined, circular, or oval in shape. Skin redness and swelling usually appear 30 minutes to 8 hours following exposure. Although they can occur elsewhere, like the mucosal area, lesions are most frequently observed in the extremities, genital, and perianal regions. After healing, the lesion site typically exhibits persistent hyperpigmentation. In FDE, ancillary systemic symptoms are not severe.The drugs mostly reported to cause Fixed Drug Eruptions are Antibiotics like (Tetracyclines, Cotrimoxazole, Metronidazole, Amoxicillin and Ampicillin); NSAIDs; Antifungals (Albendazole, Tinidazole and Fluconazole); and other drugs like Belladona, Dapsone, Allopurinol, Sulfasalazine, Benzodiazepines, Quinine and Hyoscine butylbromide.(5,11).

II. CASE SUMMARY:

A 44-year-old female came with complaints of itching with eruptions over bilateral axillae, back, abdomen, and flank pain for 3 days. Blackish discoloration with burning pain over lesion for 2 days, breathing difficulties for 3 days. Her past medical history includes Steven-Jhonson-Syndrome (SJS) in 2017 and was a known case of type II Diabetes Mellitus since 2017 and Hypothyroidism since 2018. She was on Tab. GLUFORMIN G2 (Glimepiride 2mg + Metformin 500mg) BID, Tab. TENIVA (Teneligliptin 20mg) BID, Tab. ELTROXIN (Levothyroxine 25mcg) OD. She was diagnosed with a vagina infection a few days ago and was started on Tab. FOLE (Fluconazole 150mg). She developed the above complaints after initiating this drug. The physician had a provisional diagnosis of urticaria under

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investigation. On examination, her blood pressure was 110/70 mmHg, pulse rate 84 bpm, temperature 98 (F), and spO2 98%. Her laboratory investigations showed Hb = 11.5g/dL (11.6-15 g/dL), Total Leukocyte Count (TLC)= 12650 cells/microlitre (4000-11000 cells/microlitre), Platelets= 125000 (1.5-4.5 lakh/microlitre), Random Blood Sugar (RBS)= 349 mg/dL (more than 200mg/dL), Erythrocyte Sedimentation Rate (ESR)= 70 mm/hr (<70mm/hr), Serum Creatinine= 0.6 mg/dL (0.6-1.1 mg/dL), Blood Urea= 48.3 mg/dL (6-24 mg/dL), Serum Na+= 139 mEq/L (135-145mEq/L), Serum K+= 4mEq/L (3.5-5.5mEq/L), SGPT= 29U/L (7-56U/L), CRP= 80.6 mg/dL(<0.3mg/dL). The patient was given symptomatic treatment with Tab. AVIL (pheniramine maleate) 25mg thrice a day and INJ. DEXONA (dexamethasone) 8mg thrice a day for 4 days. During the 4 days of hospitalization, she was switched to insulin HUMAN ACTRAPID instead of oral hypoglycemic agents, and continuous monitoring of blood sugar was done. A list of drugs to be avoided was provided to the patient. The patient was discharged after 4 days and her vaginal infection was already cured. She was given Tab. OMNACORTIL (Prednisolone) 10mg 4 tablets at once in the morning for 5 days, then 3 tablets at once in the morning for 5 days, then 2 tablets at once in the morning for 5 days, then 1 tablet in the morning for 5 days and then stop.

III. DISCUSSION:

Based on the patient's complaints the eruptions could be a result of her history of Steven-Jhonson-Syndrome or drug-related. As her complaints started after specifically taking fluconazole there was a suspected adverse drug reaction. De-challenge was performed and it showed definite improvement. Re-challenge was not performed. The ADR was neither predictable nor preventable as only a few cases are observed. WHO-Causality Assessment Scale showed Possible as the event had a reasonable time relationship with drug intake but could also be attributed to other pre-disposing factors like her history of Steven-Jhonson syndrome. The Naranjo Scale showed a score of 3 i.e. Possible. Figure 3.1 shows the Naranjo scale score.

Question	Yes	No	Do Not Know
1. Are there previous conclusive reports on this reaction?	+1	0	0
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0
3. Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0
4. Did the adverse event reappear when the drug was readministered?	+2	-1	0
5. Are there alternative causes that could on their own have caused the reaction?	-1	+2	0
6. Did the reaction reappear when a placebo was given?	-1	+1	0
7. Was the drug detected in blood or other fluids in concentrations known to be toxic?	+1	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0

FIGURE 3.1 NARANJO SCALE

IV. CONCLUSION:

The ADR was induced by fluconazole and the patient was treated. She was provided the below list of drugs (TABLE 4.1) to be avoided and alternatives that can be used instead.

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CLASS OF DRUG	DRUG NAMES TO BE AVOIDED	ALTERNATIVES
Antibiotics	Cotrimoxazole, tetracyclines, penicillins, erythromycin, quinolones, dapsone	Cephalosporins, aminoglycosides, carbapenems, glycopeptides, linezolid
Antimalarials	quinine	Artemisinin-based combinations
Antifungals	Azoles	Polyenes, griseofulvin, micafungin
Analgesics	All NSAIDs	Cox inhibitors, opioids, steroids
Sedatives	Benzodiazepines, barbiturates	Zolpidem, ramelteon, antidepressants, alpha 2 agonists
Antihypertensives	Calcium channel blockers, ACE-inhibitors	Beta blockers, ARBs, diuretics

REFERENCES:

[1]. Calogiuri G, Garvey LH, Nettis E, Romita P, Di Leo E, Caruso R, et al. Skin Allergy to Azole Antifungal Agents for Systemic Use: A Review of the Literature. Recent Pat Inflamm Allergy Drug Discov. 2019 Sep 19;13(2):144–57.

[2]. Grant SM, Clissold SP. Fluconazole. Drugs. 1990 Jun;39(6):877–916.

[3]. Sweetman BPharm SC, Pharmaceutical Press C. Martindale The Complete Drug Reference Thirty-sixth edition.

[4]. Debruyne D. Clinical Pharmacokinetics of Fluconazole in Superficial and Systemic Mycoses. Clin Pharmacokinet. 1997 Jul;33(1):52–77.

[5]. Jerome Z. Litt. Litt's Drug Eruptions Reference Manual. 10th ed. London and New York: Taylor and Francis Group; 2005.

[6]. Morgan JM, Carmichael AJ. Fixed drug eruption with fluconazole. BMJ. 1994 Feb 12;308(6926):454.

[7]. Lane JE, Buckthal J, Davis LS. Fixed drug eruption due to fluconazole. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology. 2003 Feb;95(2):129–30.

[8]. Heikkil H, Timonen K, Stubb S. Fixed drug eruption due to fluconazole. J Am Acad Dermatol. 2000 May;42(5):883–4.

[9]. Ghislain PD, Ghislain E. Fixed drug eruption due to fluconazole: A third case. J Am Acad Dermatol. 2002 Mar;46(3):467.

[10]. Schettini N, Corazza M, Schenetti C, Pacetti L, Borghi A. Urticaria: A Narrative Overview of Differential Diagnosis. Vol. 11, Biomedicines. MDPI; 2023.

[11]. Mahboob A, Haroon TS. Drugs causing fixed eruptions: a study of 450 cases. Int J Dermatol. 1998 Nov 9;37(11):833–8.