CASE REPORT
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Generalized Bullous Fixed Drug Eruption to Fluconazole with Positive Patch Testing and Confirmed Tolerance to Itraconazole

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ABSTRACT

Generalized bullous fixed drug eruption (GBFDE) is a specific variant of fixed drug eruption that belongs to severe cutaneous adverse reactions (SCARs) and its diagnosis is based mainly on clinical course and especially on the reoccurrence of typical bullous lesions in previous and new sites after re-administration of the offending drug. We present a well-documented case of fluconazole-induced GBFDE, with a positive patch test to fluconazole (30% weight/volume preparation) and clinical tolerance to itraconazole proven by negative oral provocation. Even in SCARs, patch testing represents a useful diagnostic tool, while oral provocation remains the gold standard in cases that an alternative but the chemically relevant drug must be administered.

Keywords: Cross reactions; Drug-related side effects and adverse reactions; Fluconazole; Patch tests

INTRODUCTION

Fixed drug eruption (FDE) is a non-immediate, type IV, drug hypersensitivity reaction characterized by the recurrence of well-defined round or oval, egg-sized patches of dusky violaceous or brownish color. The lesions reappear both at the same and at new, expanding sites after readministration of the offending medication. Although the pathogenetic mechanisms of generalized bullous fixed drug eruption (GBFDE) are not fully elucidated, T-cells are the key effector cells, since they remain in the affected areas as resident memory CD8+ T cells, which in turn explain the reoccurrence of the reaction at the same site. GBFDE is a distinct variant of FDE belonging to Severe cutaneous adverse reactions (SCARs), along with other bullous drug reactions such as Stevens-Johnson syndrome (SJS) and Toxic epidermal necrolysis (TEN).[1] Histopathology can only confirm a clinical entity within the spectrum of bullous diseases, but cannot differentiate between the distinct diseases. The confirmation of GBFDE diagnosis is therefore possible in most cases during the disease.

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Case Presentation

We report the case of a 65-year-old male presented with well-circumscribed, erythematous, and violaceous patches with a diameter ranging from 10 to 40 mm, widespread on the trunk, upper arms, and abdomen, the

thenar eminence, legs, and soles. In some of the approximately 20-30 lesions over the whole body, blisters developed on these patches followed by skin detachment, but the skin remained intact between the affected areas; oral and genital mucosal erosions were also present without accompanying dysuria or pain (Figure 1, A-D). The symptoms started abruptly, with a pinprick sensation initially, followed by intense itching and a burning sensation at the sites of skin lesions, accompanied by a 37.8°C body temperature almost 8 hours after the intake of a fluconazole tablet (100 mg) for oral candidiasis, according to his dermatologist's prescription. The patient reported similar bullous lesions-although less extended and only two in number-three months before, after the intake of fluconazole for oral candidiasis, with remission within 2 weeks and residual hyperpigmentation that gradually subsided. The lesions reappeared at the same sites they had appeared during the previous episode, as well as in adding new sites. The patient was treated with prednisolone (0.7 mg/kg/day with gradual tapering), local antiseptic (0.1% octenidine hydrochloride - 2% phenoxyethanol w/v; solution), and topical emollients on both skin and mucosal erosive lesions. The itching subsided in 1-3 days, while the erythema turned dusky, then desquamated, and finally, hyperpigmented; the sites of lesions were still visible for almost 8-10 weeks after the reaction. The personal history, as well as clinical examination and laboratory tests, excluded any underlying immunosuppressive condition as causative of the recurrent oral candidiasis. Except for a slight elevation of C-reactive protein (7.4 mg/L at referral that decreased to 1.3 mg/L after 5 days), all performed tests (total blood cell count, hepatic and renal biology, urine test) were normal.

Skin biopsy from a 3-cm nummular lesion at the abdomen revealed extensive detachment of the epidermis and formation of a subepidermal bulla with preservation of the dermal papillae in the floor, the so-called "festooning" (Figure 2A); vesicles and prominent individual keratinocyte necrosis (apoptotic keratinocytes) in the epidermis were detected, while the presence of scattered melanophages in the dermis suggested that the subepidermal bulla resulted from a marked interface reaction (Figure 2B). In addition, there was a sparse, mainly perivascular, inflammatory infiltrate in the upper dermis (Figure 2C). The constellation of histologic findings was consistent with a drug hypersensitivity reaction.

Almost 6 months after the resolution, patch tests to a) fluconazole (100 mg), b) itraconazole (100 mg) in 10% & 30% weight/volume preparations in petrolatum, and c) ketoconazole cream (2%) were performed on sites of previous lesions, utilizing normal skin as a control, according to tointernationalguidelines[2]. The tests were placed for 48 hours and skin reactions were evaluated on Day 2, Day 3, and Day 7.A positive reaction (grade 2+) to fluconazole 30% was detected at all reading times (Figure 1E), while all other performed tests were negative.

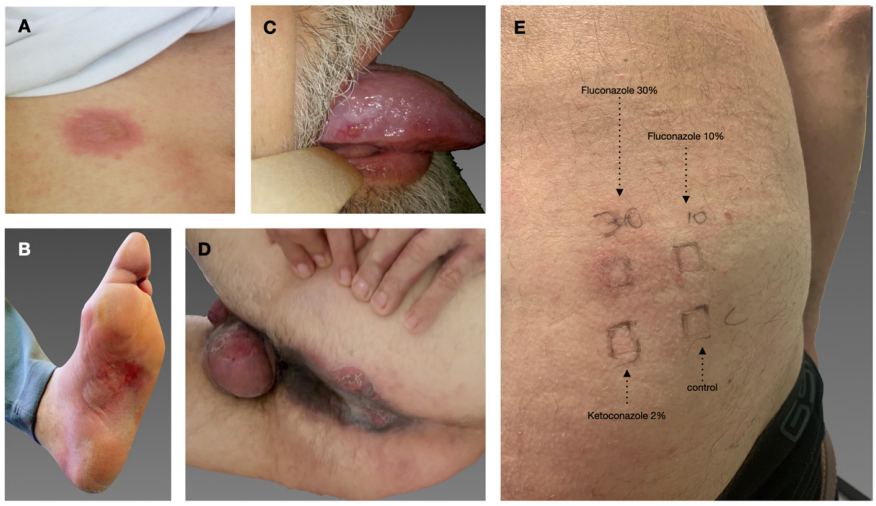

Figure 1: Generalized bullous fixed drug eruption (GBFDE) skin lesions and positive skin test to fluconazole. Typical skin (A, B: and mucosal (C, D: lesions, and the patch testing readings at 72 hours (E: upper left, 30% fluconazole)

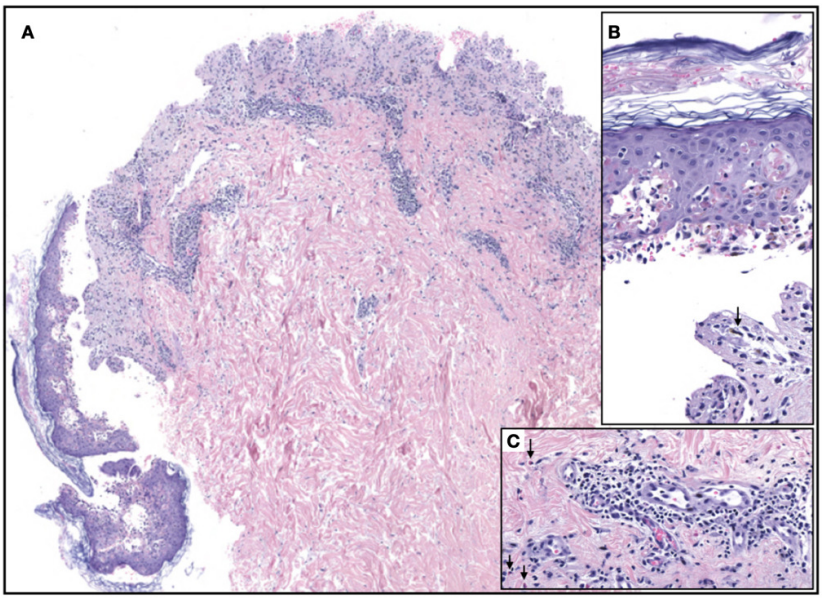

Figure 2. Histology sections A: Formation of a cell-poor subepidermal bulla with preservation of the dermal papillae in the base and a mild inflammatory infiltrate in the upper dermis (H&E, 2X), B: Vesicles and prominent individual keratinocyte necrosis (apoptotic keratinocytes) in the epidermis with a sparse monocytic inflammatory infiltrate and melanophages in the papillary dermis (black arrow)(H&E, 20X), C: Mainly perivascular inflammatory infiltrates with scattered eosinophils (black arrows)(H&E, 20X).

A subsequent single-blind oral provocation to itraconazole 100 mg was negative, confirming the clinical tolerance to this alternative antifungal agent. The patient provided informed consents for both the drug provocation and the submission of his case with photographic material.

DISCUSSION

While FDE represents a relatively common drug hypersensitivity reaction, attributed to more than 100 medications, GBFDE is a quite rare form that may resemble SJS or TEN and could also raise the risk of a potentially fatal outcome. Distinguishing GBFDE from SJS/TEN is of high salience and based almost exclusively on clinical manifestations; as shown in our case, GBFDE has a rapid onset of symptoms within less than 24 hours, mild mucosal involvement with unaffected ocular mucosa in most cases, milder systemic symptoms as fever and malaise, and finally, a much more favorable natural course and prognosis.[3]

Among the numerous drugs related to FDE occurrence, trimethoprim-sulfamethoxazole, nitroimidazoles, fluoroquinolones, and NSAIDs are the ones most often implicated. In GBFDE, on the other hand, antibiotics (metronidazole, rifampicin) and analgesics (ibuprofen) are considered the most common causes.[4]

The use of patch testing for the diagnosis of delayed SCARs still lacks standardized methodological approaches and particularly consistency with regards to the recommended drug concentrations. Contrary to US experience, which is very limited regarding drug patch tests, in Europe, the method is fairly standardized, by using commercially available patch test chambers appropriate for the type of vehicle.[5] Although the stability of patch tests for different drugs has not been validated and they are most optimally prepared just before testing, the interpretation of the results for the causative and alternative drugs in combination with the clinical history greatly contributes to the clinical decision making.[3] In combination with skin testing when applicable, in a drug-allergy context, oral provocation is still considered the gold standard diagnostic procedure for the determination of the culprit drug; however, it is contraindicated in FDE, due to the risk of extensive FDE or GBFDE.

The azoles include compounds with different actions, such as antiprotozoal and antibacterial (nitroimidazoles: metronidazole, tinidazole, secnidazole) and antifungal ones (imidazoles: ketoconazole, miconazole, clotrimazole; and triazoles: fluconazole, itraconazole, voriconazole). Fluconazole has rarely been associated with FDE and less than 30 cases have been published in PubMed indexed journals to date.[6]

Awareness of cross-reactivity is important in FDE, as patients should be informed about other similar medications that may increase the likelihood of a recurrence. Cross-reactivity among members of the antifungal triazoles and imidazoles and between these two groups has been reported, but no consistent pattern of cross-reactivity has been described.[7,8] The pattern of tolerance to itraconazole in a confirmed case of fluconazole-induced generalized FDE was documented with the use of a lymphocyte transformation test and a drug provocation test in a recent case.[9]

To our knowledge, this is the first case in literature that presents fluconazole-induced GBFDE with positive patch testing to fluconazole and negative to itraconazole, and a subsequent negative oral provocation test to itraconazole. All previous reports refer to FDE,[6,8,10] while in all cases in which patch tests to fluconazole 10%[8,10] and 30% in petrolatum[9] were performed, no positive result was observed. In contrast, in our case, 30% of the fluconazole patch tests turned positive. GBFDE and especially the more severe cases of it represent a unique drug hypersensitivity reaction that remains far from evident, without many well-documented reports.

In conclusion, GBFDE represents a severe form of drug hypersensitivity reaction; its occurrence excludes the re-administration of the offending drug. Patch testing with offending and alternative agents -when performed properly- may contribute to the selection of a safe alternative therapeutic option. The safety of the alternative must be confirmed by oral provocation.

CONFLICT OF INTEREST

All authors state that they have no conflict of interest to declare

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The authors have nothing to declare

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