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CASE REPORT

A case of tadalafil-induced fixed drug eruption

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ABSTRACT

Fixed drug eruption is a variant of adverse cutaneous drug eruptions which is characterized by the formation of dusky patches and plaques involving the skin and mucosa, following the ingestion of certain drugs such as non-steroidal anti-inflammatory drugs, metronidazole and cotrimoxazole. Herein, we would like to report an unusual case of tadalafil-induced fixed drug eruption.

Keywords: drug eruptions, phosphodiesterase 5 inhibitors, skin

INTRODUCTION

Fixed drug eruption (FDE) is a type of cutaneous adverse drug eruptions characterized by the emergence of single or multiple erythematous-to-purpuric, nummular patches and plaques after exposure to certain drugs [1]. The skin lesions tend to recur each time at the same localization with the consumption of that particular medication [1]. The cutaneous eruption begins within weeks after the drug exposure, however rapid reappearance of the lesions occurs within 1 or 2 days following the repeated ingestions. The most frequently affected sites are limbs, hands, feet and mucosae [1]. A study from France which encompassed three year evaluation of FDE, paracetamol and other non-steroidal anti-inflammatory drugs were the most commonly implicated medications [1]. Herein, we would like to report an uncommon case of FDE following tadalafil ingestion.

CASE PRESENTATION

A 51-year old man was seen at the dermatology outpatient clinic due to multiple, enlarging, non-pruritic skin eruption seen upon the lower extremities. The lesions had begun two days ago in the form of small red papules which later turned into hyperpigmented plaques. Dermatological examination revealed multiple, well-circumscribed, erythematous-to-purpuric patches and plaques involving the lower legs and inner ankles (Figure 1). There were no associated pruritus or pain and no mucosal involvement was present. The patient did not have any other systemic disease and was not using any regular medication. However one day prior to the onset of the skin lesions, he took 5 mg tadalafil pill to enhance intercourse satisfaction. He denied any other recent drug intake other than tadalafil. The patient was using tadalafil on occasion and he recalled that he had developed similar

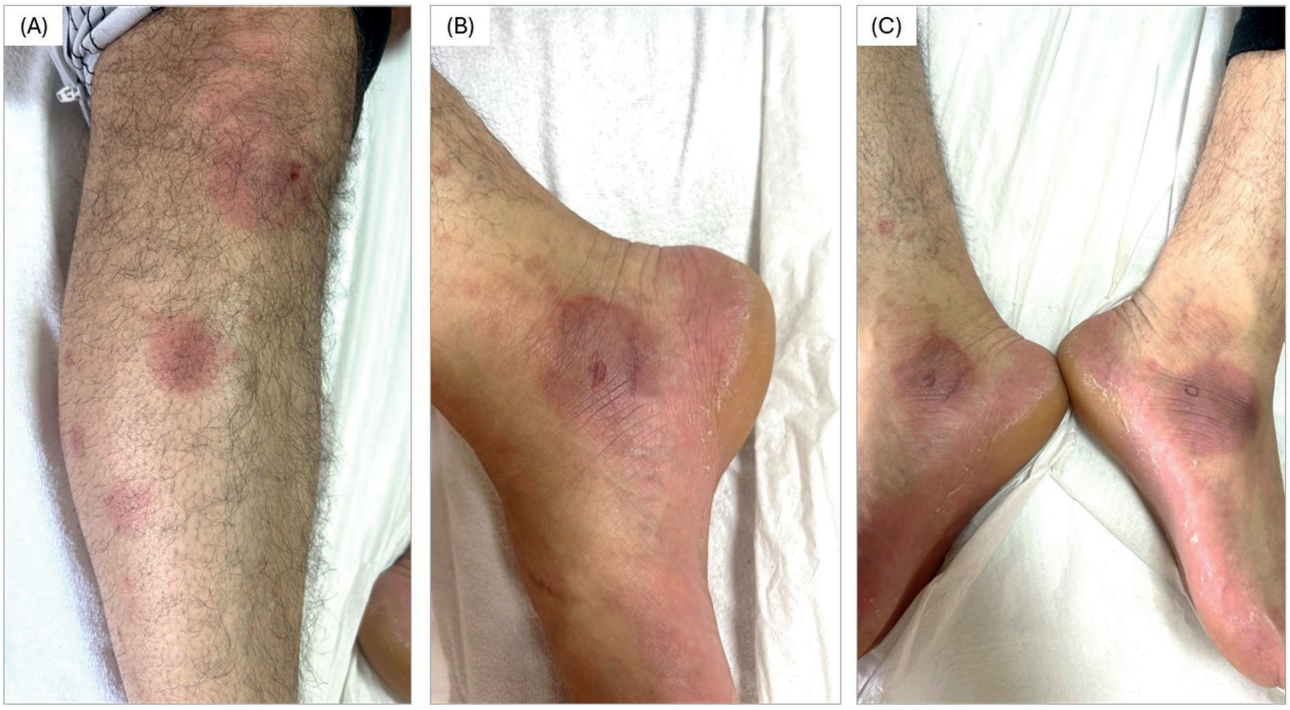

Figure 1. Well defined, erythematous patches and plaques with central violaceous color change present upon the lower extremities (A) and inner ankles (B,C).

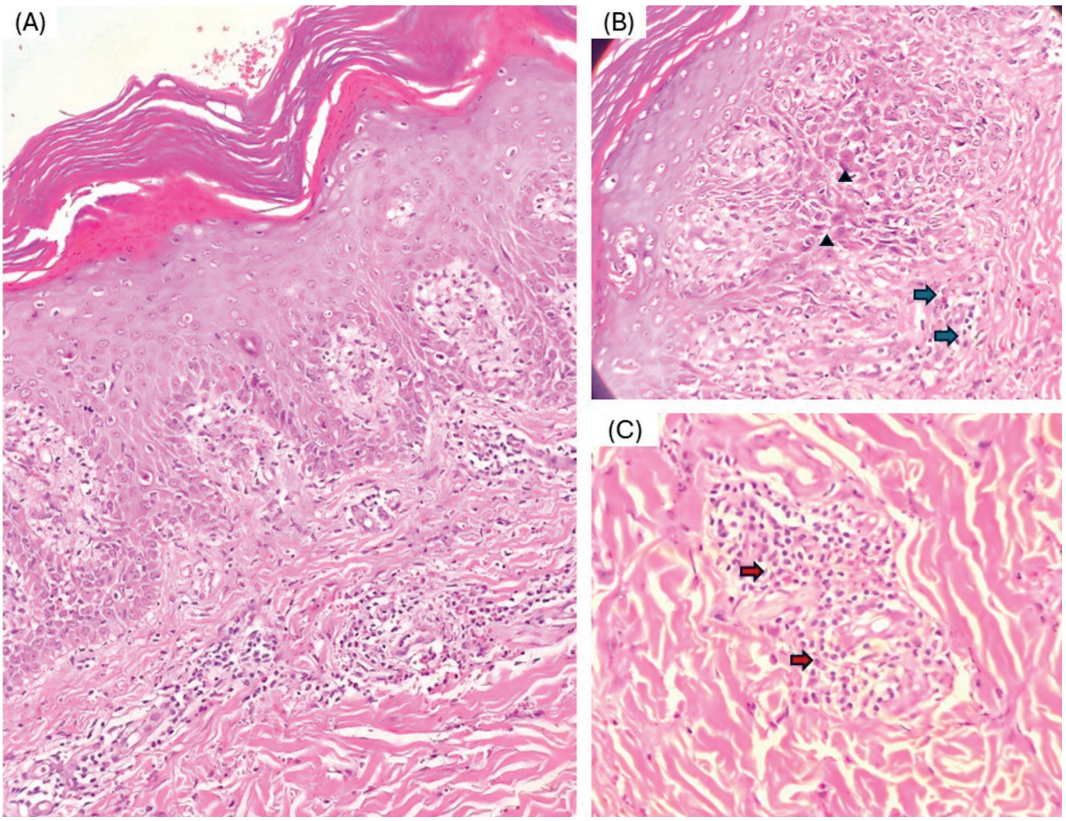

Figure 2. (A) The epidermis has patchy parakeratosis. Scattered necrotic keratinocytes with eosinophilic cytoplasm and pyknotic nuclei are seen in the epidermis. There is superficial and deep dermal perivascular lymphocytic and eosinophilic infiltrate (H&E, x200). (B) Epidermal necrosis and colloid body formation are seen (arrowheads), and dermal lymphocytic and eosinophilic infiltrate (blue arrows) (H&E, x400). (C) Dermal perivascular lymphocytic and eosinophilic infiltrate (red arrows) (H&E, x400).

eruption located at the same locations once again, when he had taken tadalafil previously. Based on the clinical history and dermatological examination findings, FDE was the initial diagnosis. According to the Naranjo Adverse Drug Reaction Probability Scale [2], the present case received a total score of 5 [Are there previous conclusive reports on this reaction? (1 point); Did the adverse event appear after the suspected drug was administered? (2 point); Did the adverse reaction improve when the drug was discontinued? (1 point); Was the adverse event confirmed by any objective evidence? (1 point)] which points out to a 'propable' drug reaction caused by tadalafil. Due to the feasibility restrictions, we were not able to perform an oral provocation or patch testing, which was the limitation of the present report. Skin biopsy was taken and histopathological examination showed scattered necrotic keratinocytes with eosinophilic cytoplasm and pyknotic nuclei in the epidermis, a lichenoid infiltrate composed of lymphocytes and eosinophils in dermis along with superficial and deep dermal perivascular lymphocytic and eosinophilic infiltrate (Figure 2). The diagnosis of FDE was confirmed. Topical application of mometasone furoate ointment and urea-containing emollient for two weeks resulted in the regression of the lesions; minimal residual hyperpigmentation was noted at the end of tenth day. The Informed consent was taken from the patient for the publication of the case details.

DISCUSSION

FDE is a sort of delayed-type of hypersensitivity reaction which is mediated by CD8+ memory cells settled in the epidermis [3]. The distinctive feature of FDE is the repetition of the erythematous, hyperpigmented or bullous skin lesions at the same body localization following the exposure of a particular drug. According to a 20-year cross-sectional study which included 191 patients from Türkiye; cotrimoxazole, naproxen, metronidazole/ornidazole, piroxicam/tenoxicam and dipyrone were among the most common causative drugs of FDE [4]. Another study which investigated 182 adult FDE patients from Türkiye between the years 1996-2018, showed that non-steroidal anti-inflammatory drugs and trimethoprim-sulfamethoxazole were the most frequently blamed agents [5]. Tadalafil is a phosphodiesterase-5 inhibitor generally used for erectile dysfunction or increasing coital pleasure and erection time.Tadalafil-induced FDE cases were reported rarely in the literature; the clinical features

Table 1. The summary of the some reported tadalafil-induced fixed drug eruption in literature with comparison to the present case

Parameter	The present study	Bjekic et al. [6]	Sarawgi & Rudra [7]	Zhang et al.[8]	Das et al.[3]
Age (years)	51	30	46	29	Case 1: 36 Case 2: 17
Sex	Male	Male	Male	Male	Male
Recurrent drug exposure	Yes	Yes	Yes	Yes	Case 1:Yes Case 2: Yes
Multiple/single lesions	Multiple	Multiple	Multiple	Multiple	Case 1:Multiple Case 2: Single
Localization of skin lesions	Lower extremities, ankles	Penile shaft, oral mucosa, elbow, elbow, periorbital lesion	Lip, chest, back, upper and lower extremities, genitalia, buttocks	Oral mucosa, arm, legs, penis, hand and feet	Case 1: Glans penis Case 2: Tongue
Time between the drug exposure and skin eruption	24 hours	-	A few days	Hours	Case 1: A day Case 2: ---
Any accompanying symptom	None	Mild pruritus	Itch and mild pain	Pain	Case 1: Mild tender Case 2: Mild pain
Intervention	Topical mometasone furoate ointment and urea-containing emollients	Topical corticosteroid therapy and gingival hyaluronic acid 0.2% gel	Oral prednisolone	Topical triamcinolone 0.1% ointment	Case 1: A low potent topical steroid Case 2: N/A

along with the characteristics of the some patients reported in the literature are shown in Table 1. The offending drugs such as cotrimoxazole, naproxen and tadalafil act as haptens that attach to the basal keratinocytes and create an inflammatory response by inducing CD8+ T cell expansion and production of cytokines [3]. As clearly seen Table 1, the elapsed time between the start of FDE and drug exposure is usually short (hours to a few days) and skin lesions tend to be multiple [3-8], even though a case reported by Das et al. [3] presented by a single erosion upon the corner of the tongue. Even though, no mucosal involvement is observed in our patient, the reported cases in the literature presented with one or more mucosal site involvement [3-8]. Therefore, FDE can easily be confused with venereal diseases, autoimmune bullous diseases and other drug eruptions such as Stevens-Johnson syndrome. The accurate diagnosis of FDE along with abrupt interruption of the offending medication is significant in the management of FDE.

All in all, we would like to emphasize that tadalafil can be a cause of FDE by inducing the formation of recurrent, fixated violaceous to hyperpigmented, nummular patches and plaques involving the skin and mucosa.

Author contribution

Study conception and design: EB and FG; data collection: EB and FG; analysis and interpretation of results: EB; draft manuscript preparation: EB. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

Infomed consent was taken from the patients for the publication of the case details and images.

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Conflict of interest

The authors declare that there is no conflict of interest.

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