A case of bullous fixed drug eruption caused by tadalafil

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Key words: drug reactions; fixed drug eruption; tadalafil.

INTRODUCTION

Fixed drug eruption (FDE) is a cutaneous adverse drug reaction characterized by the emergence of erythematous to violaceous, round to oval patches with a dusky center at a fixed location following the ingestion of specific medications.[1] In some instances, these lesions may also manifest as vesicles and/or bullae.[1] FDE can present as solitary, multiple, or generalized lesions. While the onset of FDE after drug ingestion can occur within weeks, it may develop within 48 hours, especially for cases of re-exposure. Though acute inflammation subsides within days to weeks, postinflammatory hyperpigmentation may persist.[1] FDE can be triggered by a wide range of drugs, which have been well-documented in the literature. Notably, tadalafil, a phosphodiesterase 5 inhibitor FDA-approved for treating erectile dysfunction and benign prostatic hyperplasia, has recently been reported in 3 cases. While it is legally available only by prescription, it can be acquired by numerous other methods and has been found in over-the-counter honey-based sexual enhancement supplements.[2]

We present here a case of bullous FDE likely caused by tadalafil. According to literature review, this represents the fourth reported case of FDE associated with tadalafil exposure. However, unlike the other cases, in this 1, the patient's skin lesions can be attributed to tadalafil in an over-the-counter supplement. This case underscores the significance of obtaining a comprehensive patient history, including the use of over-the-counter supplements and non-prescribed medications, to ascertain the source of cutaneous drug reactions.

Abbreviations used:

ANA:	anti-nuclear antibody
DIF:	direct immunofluoresence
EM:	erythema multiforme
FDE:	fixed drug eruption
H&E:	hematoxylin and eosin
PCR:	polymerase chain reaction

CASE REPORT

A well-appearing 29-year-old male presented to dermatology clinic with painful bullae that appeared 4 days earlier, 1 hour after taking liquid tadalafil obtained from a friend. Previously, he experienced similar, self-resolving lesions within hours of consuming an over-the-counter honey-based sexual enhancement supplement. A thorough review of systems was negative. Positive physical exam findings of his skin, oral mucosa, and eyes included hyperpigmented patches of the mucosal lips, penis, arms, legs, dorsal hands, and dorsal feet (Fig 1). Small to large targetoid lesions consisting of either a central bulla or dusky patch surrounded by a violaceous to erythematous rim, were visible on the arms, legs, dorsal hands, and dorsal feet in a symmetric distribution (Fig 1).

Two 4 millimeter punch biopsies were performed on the left upper arm. The first was taken at the edge of a tense bulla for H&E, while the other was obtained from a perilesional site 1 centimeter away for DIF. H&E revealed a subepidermal bulla with epidermal necrosis, vacuolar interface changes, and rare eosinophils (Fig 2). Scattered cytoid bodies were seen on DIF. Other blistering disorders were ruled out with the DIF findings, a negative pemphigoid

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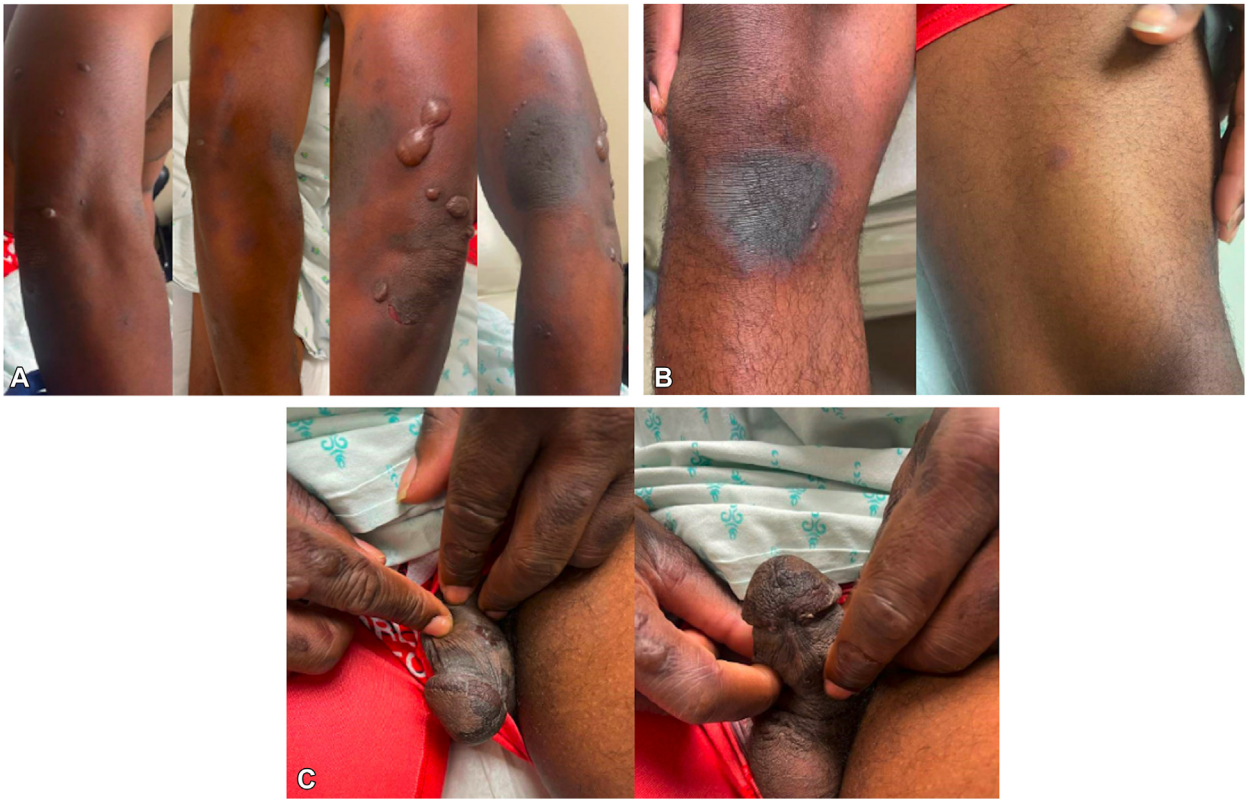

Fig 1. **A,** Bilateral upper extremities in symmetric distribution: scattered small to large targetoid lesions with central tense vesicles and bullae each with a surrounding violaceous/dusky rim along with scattered hyperpigmented, violaceous round macules and patches. **B,** Large annular targetoid patch with dusky center and surrounding violaceous border on the *right* knee and a similar smaller lesion on the *left* thigh. **C,** Healing erosions on the penile shaft and hyperpigmented patches and plaques of the glans and penile shaft.

antibody panel, and negative collagen type VII IgG. Tissue PCR for herpes simplex virus (HSV) 1 and 2 were negative. ANA was also negative.

Although a prescription for clobetasol 0.05% ointment was sent for the patient to use on affected areas, he did not pick up the medication. Given concern for HSV in the setting of possible recurrent EM, acyclovir 800 mg twice daily was started prophylactically. At a follow-up appointment a month later, the patient reported no additional outbreaks. Exam was positive only for postinflammatory hyperpigmentation in areas with previous blisters. We emphasized the importance of avoiding the honey-based sexual enhancement supplements as well as tadalafil, which we explained was the likely culprit. The patient was started on triamcinolone 0.1% ointment twice daily and instructed to follow up as needed. He has not returned to the clinic since. The combination of the clinical presentation, the histologic findings, and laboratory tests aligned with a diagnosis of fixed drug eruption due to tadalafil.

DISCUSSION

Generalized bullous fixed drug eruption, an extensive eruption of bullae, can be a life-threatening condition,[3] thus making accurate diagnosis critical. Making the diagnosis posed a significant challenge in this patient. The timing of lesion onset following drug exposure and the distribution of the skin lesions all exhibited characteristics that can be seen in both bullous EM and bullous FDE.[2,4,5] Furthermore, the histologic findings mentioned above characterize both bullous EM and bullous FDE. While the presence of deep inflammation, deep melanophages, eosinophils, and neutrophils are more typical of FDE than EM, the diagnosis should not be made based on pathology alone. The clinical morphology of the large atypical oval targets are more suggestive of FDE.

In 1 reported case of localized FDE to tadalafil, a 30-year-old man developed erythematous patches affecting the penile shaft first followed by the patches in right forearm and left periorbital region.[6] In another case of generalized bullous FDE to tadalafil, a 46-year-

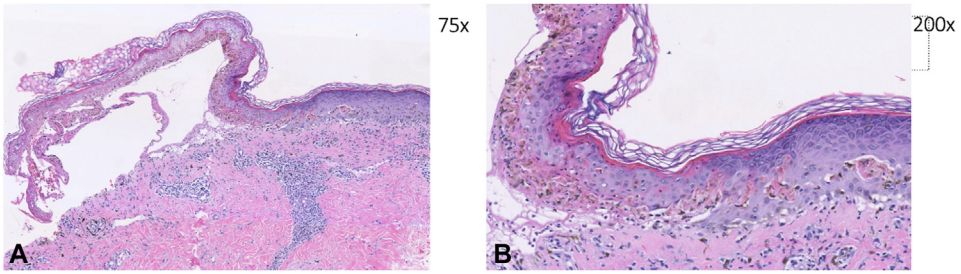

Fig 2. **A,** Subepidermal bulla with acute vacuolar interface-mediated epidermal necrosis (H&E, 75×). **B,** Vacuolar interface changes with dyskeratotic cells, clusters of intraepidermal apoptotic bodies, and rare eosinophils (H&E, 200×). *H&E*, Hematoxylin and eosin.

old man experienced 3 similar events of multiple itchy erythematous patches with blisters in the same locations including his lips, chest, and upper limb.[7]

Over-the-counter supplements containing active drug ingredients pose a threat to the safety of the general public due to lack of standardization. As these supplements do not require regulation through the Food and Drug Administration (FDA) for safety, effectiveness, or accurate marketing of included ingredients, they bypass the need for prescription or counseling from a trained medical provider. Lack of counseling or transparent information about product ingredients increases the risk of adverse effects, including the 1 experienced in this case. In 2022, the U.S. Food and Drug Administration (FDA) warned a few companies about illegally selling honey-based products containing active drug ingredients (including tadalafil) not listed on product labels. As seen in this case, the unmonitored use of both liquid tadalafil and a non-FDA approved honey-based sexual enhancement supplement that hid its active ingredient proved to be inciting factors in the development of our patient's cutaneous reaction. If suspecting FDE, questions about over-the counter supplements and nonprescription medications should not be missed.

Conflict of interest

None disclosed.

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