Bullous fixed drug eruptions consequent to NSAID usage – a case series

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Fixed drug eruption (FDE) is a distinct, delayed type-IV hypersensitivity manifesting as recurring cutaneous reaction (on skin or mucosa) in the same locations on re-exposure to the offending drug. This is most commonly due to oral medications, antimicrobials and NSAIDs being the most common culprits. Herein, we discuss six cases of bullous FDE due to diverse NSAIDs. The first case was Naproxen-induced bullous fixed drug eruption (BFDE), the second case was due to Etoricoxib, the third patient had Mefenamic acid-induced BFDE, the fourth was Ibuprofen-induced FDE, the fifth one was Diclofenac-induced BFDE, the sixth was Aceclofenac-induced BFDE, and the seventh was a case of paracetamol-induced BFDE. All these patients noticed skin reactions that were clinically diagnosed by the dermatologist as NSAID-induced BFDE. The mainstay of treatment adopted was to avoid the culprit drug. All the seven patients were treated with oral steroids, followed by antihistaminics for reducing FDE-associated pruritus, ointment soframycin, and topical steroids for hyperpigmented lesions. Prompt diagnosis of BFDE and drug withdrawal at the clinician side may help in rapid resolution of the reaction within days to delayed recovery within few weeks, thus preventing rise in morbidity and mortality.

Keywords:
adverse drug reaction, bullous fixed drug eruption, cluster-differentiation cells, hyperpigmentation, NSAIDs

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Introduction

Fixed drug eruptions (FDE) can be typically a single well demarcated, pruritic, round or oval red, or violaceous patch or plaque on the skin or mucous membrane that may blister or ulcerate occurring at the same 'fixed' location on repeated exposure to any chemical substance or drug. It is mostly asymptomatic, but it can be painful and itchy. Before peeling over the next few days and weeks, the surface may become scaly or crusted and eventually fades to leave brown postinflammatory hyperpigmentation, which is more prominent in people with fair complexion. In the majority of drug eruptions, the patient remains systemically healthy [1]. Rarely, FDE may be food-related as in meat products with residual antibiotics and tonic water containing quinine. Interestingly, the gene human leukocyte antigen -B22 is said to be linked to the risk of developing a FDE [2].

Hands, feet, eyelids, and anogenital areas are common locations of FDE. Oral mucosa lesions are typically found on the lips, tongue, and hard palate. The commonest FDE-causing drugs are antimicrobials (penicillins, cotrimoxazole, tetracycline, and erythromycin), next to analgesics like aspirin, diclofenac, naproxen, and ibuprofen [3,4]. The eruption may occur after weeks to years of regular ingestion of the drug on the first occasion, but subsequent episodes occur within minutes to hours of resuming the implicated drug. A patch of FDE exhibits a refractory period during which it does not flare even after re-exposure. The original patch may enlarge in subsequent episodes, and new patches may appear. With each recurrence, the postinflammatory hyperpigmentation darkens [5]. Bullous drug eruptions can be classified into the following main categories based on the various mechanisms:

(1) Spongiotic or eczematous.
(2) Acute generalized exanthematous pustulosis.
(3) Erythema multiforme.
(4) FDE.
(5) Stevens–Johnson syndrome (SJS).
(6) Toxic epidermal necrolysis (TEN) [6].

FDE is usually a cluster-differentiation (CD8)-mediated lymphocytic reaction, in which the culprit drug reactivates memory T lymphocytes in the dermal and intraepidermal tissues causing local sequelae. Generally, within 30 min, local reactions flare up and continue up to one day of drug re-exposure [3]. The cytotoxic (memory CD8+) T cells release interferon-gamma in the initial phase at the dermo-epidermal junction when activated by the antigen, causing damage to the basal layer of the epidermis. The T cells and neutrophils may harm the melanocytes and keratinocytes. Dermal macrophages collect melanin during the resolution phase, resulting in the typical postinflammatory hyperpigmentation [7]. Majority of the drug-induced cutaneous ADR reports are only suspected but not confirmed cases, thus making pharmacovigilance more challenging. Furthermore, without specific diagnostic tests, adverse reactions are rarely specific to the drug, and a rechallenge is ethically not justified [8].

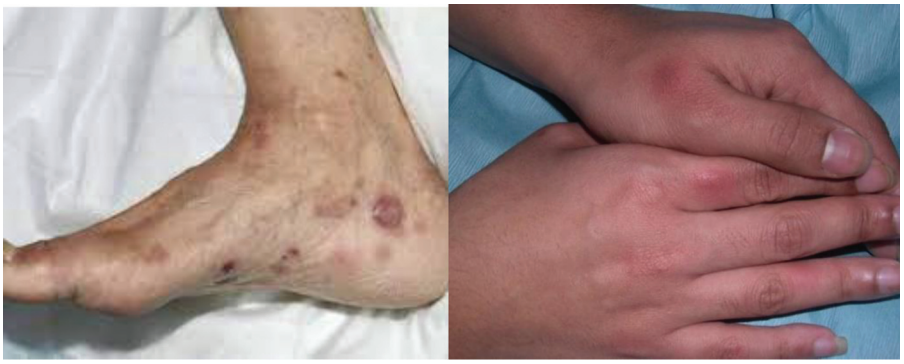
Case report 1

A 43-year-old female came to the Dermatology Department with complaints of fluid-filled lesions on both lower limbs and solid elevated lesions on the dorsum of both hands for the last 3 days. The lesions appeared after the patient took tablet Naproxen 500 mg as self-medication for osteoarthritis. This case was diagnosed as Naproxen-induced bullous fixed drug eruption (BFDE) and the drug was stopped right away and the patient was treated for the cutaneous ADR. She was counseled to keep a drug-allergy card to avoid such mishap in future (Figures 1 and 2).

Case report 2

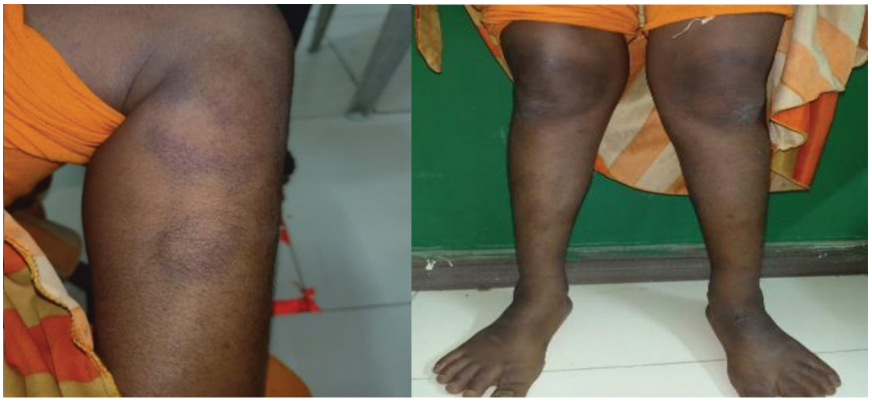
After taking tablet Etoricoxib 90 mg for postoperative dental surgery pain for 7 days, a 34-year-old female presented to the Dermatology Department with deep erythematous flat lesions over both lower limbs, oral erosions with discomfort over the lesions, itching, burning sensations, and fever. Her lower limbs, face, oral cavity, buccal mucosa, hard palate, nails, and genitalia were all covered with nodular hyperpigmented lesions. She had no relevant medical history. This was diagnosed as Etoricoxib-induced BFDE. She was treated with oral corticosteroids and cautioned to avoid using the same drug in future (Figures 3 and 4).

Figure 1



Case 1: Naproxen-induced bullous FDE.

Figure 2

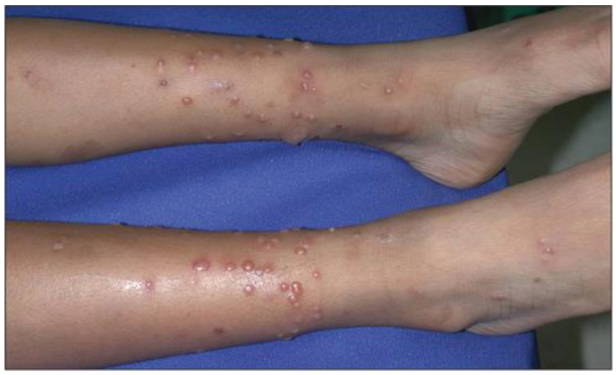


Case 2: Etoricoxib induced bullous FDE.

Case report 3

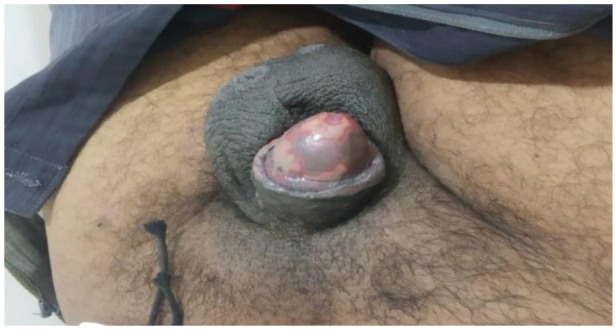
A 24-year-old female patient was admitted to the DVL Department with a complaint of fluid-filled lesions over both lower limbs after taking capsule Mefenamic acid 500 mg for pain relief for 10 days. On the basis of dermatological examination, she was diagnosed to have Mefenamic acid-induced BFDE, the drug was stopped and she was treated with tablet cefuroxime 250 mg, but the reaction subsided within few days (Figure 5).

Figure 3



Case 3: Mefenamic acid induced bullous FDE.

Figure 4



Case 5: Diclofenac induced bullous FDE.

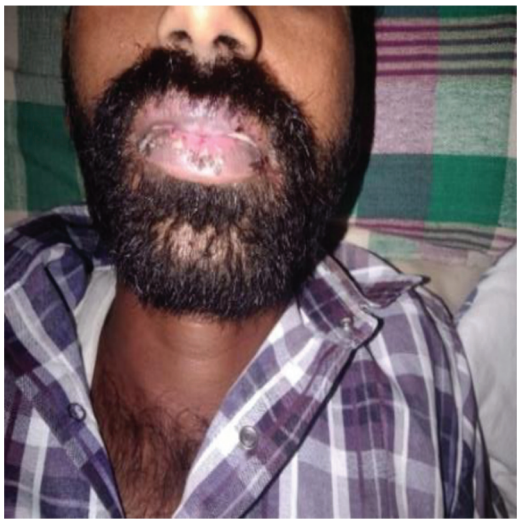
Case report 4

A 30-year-old female patient visited the Dermatology OPD suffering with pus-filled painful pustules over the face and rashes over the upper limbs after taking tablet Ibuprofen 400 mg for 1 week as 'over the counter' (OTC) drug. Her case was diagnosed as Ibuprofen-induced BFDE and the culprit drug was stopped. She was treated with tablet deflazacort 6 mg and cream Fucibet (Fusidic acid 2% and Betamethasone 0.1%) and recovered within 10 days (Figures 7–9).

Case report 5

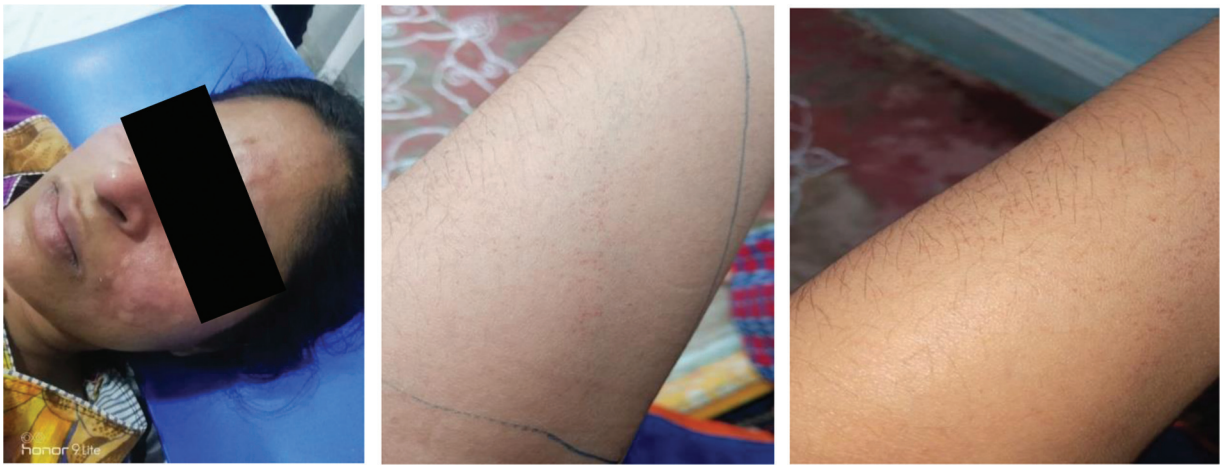
A 46-year-old male patient came to DVL who experienced lesions and erosions over the penis for

Figure 6



Case 6: Aceclofenac induced bullous FDE.

Figure 5



Case 4: Ibuprofen induced Bullous FDE.

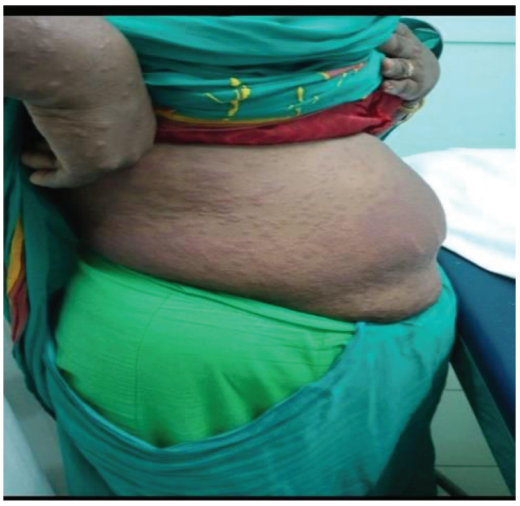
the last 2 months on self-medicating with tablet Diclofenac Sodium 100 mg oral for pain relief. This was diagnosed as Diclofenac Sodium-induced BFDE and the drug was withdrawn. He was treated with tablet Deflazacort 6 mg, cream Fucibet (Fusidic acid 2% and Betamethasone 0.1%), tablet Cefixime 200 mg, tablet Hydroxyzine 10 mg, and recovered within 2–3 weeks (Figure 6).

Case report 6

A 33-year-old male patient with fever was prescribed tablet Aceclofenac 100 mg oral for 3 days by the local RMP. He developed fluid-filled blisters on buccal mucosa after 10 days of drug administration, which then spread to the lips. Blisters ruptured to form erosions, which later healed with crusts for almost 20 days. He then consulted a dermatologist who diagnosed the case as Aceclofenac-induced BFDE. He was treated with intravenous injection Decadron (Dexamethasone), tablet

*Omnacortil 5 mg (p*rednisolone), *Tosti gel* 5 g (triamcinolone), Capsule Oxidon Plus, and *Mucopain Gel* (Benzocaine 20%). He recovered in a week's time (Figure 10).

Figure 7



Case 7: Paracetamol induced bullous FDE.

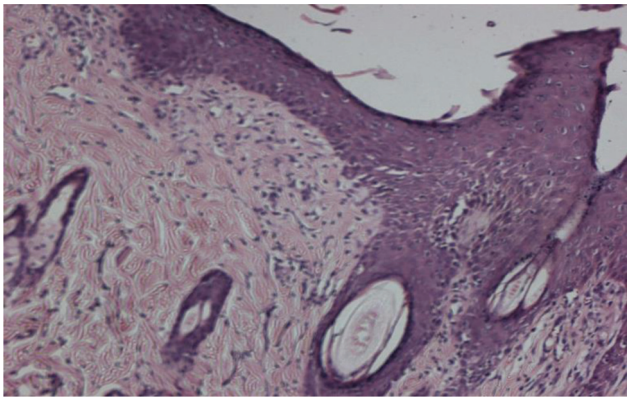
Case report 7

A 48-year-old female patient with backache took tablet paracetamol 650 mg (Acetaminophen) oral for 7-day OTC. She developed painful pustules, rashes over the upper limbs and abdomen after taking the tablet for 1 week as OTC drug. Her case was diagnosed as paracetamol-induced BFDE and the culprit drug was discontinued (Figure 11).

Results and discussion

FDEs are delayed allergic reactions occurring at the same cutaneous site as a result of repeated ingestion of an offending drug [9]. According to recent Indian research, almost 20–43% of all cutaneous ADR are FDEs [10]. Cutaneous ADRs occur in ~1–2% of cases. HIV patients may be more susceptible to adverse cutaneous drug reactions [11]. The reaction severity may worsen with multiple exposures to the same offending drug, and in rare cases, progress to a clinical state known as generalized BFDE, which has numerous large, violet-colored livid patches and sometimes, flaccid blisters may be wrongly diagnosed

Figure 8



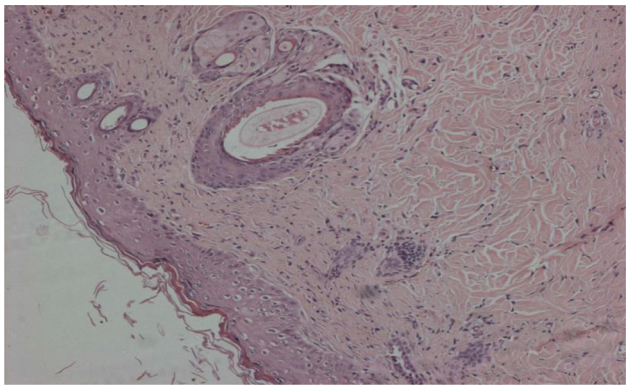
Histological examination: keratinocyte necrosis And diffuse lymphocytic inflammatory infiltrate in BFDE.

Table 1 Summary of seven cases of NSAID-induced bullous fixed drug eruption

	Offending drug	ADR	Temporal association	Dechallenge	Rechallenge	Causality assessment using WHO– UMC scale	Outcome
Case 1	Naproxen	Bullous FDE					
Case 2	Etoricoxib	Bullous FDE					
Case 3	Mefenamic acid	Bullous FDE					
Case 4	Ibuprofen	Bullous FDE	Present	Positive	Not done	Probable	Recovered
Case 5	Diclofenac	Bullous FDE					
Case 6	Aceclofenac	Bullous FDE					
Case 7	Paracetamol	Bullous FDE					

FDE, fixed drug eruption.

Figure 9



Complete re epithelization with normal epidermal layer of erupted region after treatment.

clinically as SJS or TEN (Figures 12 and 13). When an offending drug is reused, the reappearance of lesions over previously affected sites serves as a diagnostic marker. Lesions heal quickly and without complications, resulting in residual hyperpigmentation [12]. It may be difficult to differentiate generalized BFDE from SJS and TEN on the basis of histopathology. In all three conditions, changes on the skin range from a few scattered necrotic keratinocytes to full-thickness epidermal necrosis, which is indistinguishable clearly [13]. Eosinophil infiltration and pigment incontinence with absent fire-flag sign (more than two aggregated dyskeratotic keratinocytes in the epidermis is fire-flag sign positive seen in SJS/TEN) is the hallmark of generalized BFDE differentiating it from SJS/TEN [14].

The mechanism of localized FDE is immunologically mediated inflammatory response wherein drug-specific memory CD8+ T cells localized and fixed in a particular cutaneous region are preferentially activated [15]. Upon discontinuation of the medication in an FDE case, the cutaneous eruption will be downregulated by the abundant CD4+ T cells [2]. When the offending drug is removed, the majority of bullous drug eruptions resolve without significant sequelae. Use of topical steroids, emollients, and oral antihistaminics are a part of the general ADR management. The morbidity of these reactions, on the other hand, is directly related to the extent of involvement of skin surface and mucous membrane [16].

NSAIDs exert analgesic, anti-inflammatory action by inhibiting cyclooxygenase enzyme and block the release of prostaglandins and other chemical messengers that are responsible for pain and inflammation [17].

All seven cases of BFDE were treated with oral steroids (prednisolone) followed by antihistaminics, local soframycin, and topical steroids for hyperpigmented lesions, and were in good health post recovery. Causality assessment was done in these patients with the help of WHO–UMC scale and diagnosed as probable cases of NSAID-induced BFDE. It is possible to avoid severe and preventable ADRs by creating alertness among the treating clinicians about drugs implicated in BFDE (Table 1).

Conclusion

Pharmacovigilance is an essential tool for practicing physicians in detecting and diagnosing ADR. Voluntary ADR reporting by clinicians is critical in the detection and prevention of adverse drug reactions and helps lowering treatment costs. Those with a history of drug allergy and genetic variations of human leukocyte antigen – B22 should absolutely abstain from using such BFDE-causing medication. FDE in usual cases is not severe but raises cosmetic concerns, specifically when residual hyperpigmentation occurs because of recurrence on the same site [3]. Raising awareness among the clinicians regarding cautious prescribing of NSAIDs, which may cause BFDE, will be the call of the hour, so that safer alternate drugs may be preferably prescribed and preventive measures can be scaled up.

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All authors have done equal contributions in preparing and revising this paper content. All authors approved the final paper.

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Conflicts of interest

There are no conflicts of interest.

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