Letter to the Editor
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Two cases of generalized bullous fixed-drug eruption triggered by etodolac

Etodolak ile tetiklenen generalize büllü fiks ilaç erupsiyonlu iki olgu

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Anahtar Kelimeler: Jeneralize büllöz fiks ilaç erüpsiyonu, büllöz fiks ilaç erüpsiyonu, NSAİİ, etodolak

Dear Editor;

Fixed-drug eruption (FDE) is a common allergic reaction to medications and characteristically recurs at the same skin site by each use of the offending drug. It is characterized by well-defined red to purplish macular lesions. Rarely, urticarial, bullous, targetoid, and purpuric lesions are observed[1]. It occurs most frequently after the oral administration of the causative drug. However, rare cases were reported after intravenous, intramuscular, or topical administration. Generalized bullous fixed-drug eruption (GBFDE) is a very rare variant. Toxic epidermal necrolysis (TEN) and Steven-Johnson syndrome (SJS) are the main diseases that must be differentiated, particularly in cases with mucosal involvement[2]. The latency period between the intake of the offending drug and the onset of reactions varies from hours to days. The most common triggers for GBFDE include sulphonamides and analgesics, and other antibiotics and antiepileptic drugs are less frequently reported[2,3].

Non-steroid anti-inflammatory drug (NSAID)-induced hypersensitivity reactions involve different mechanisms and present a wide range of clinical manifestations from anaphylaxis to delayed-type responses. Etodolac, a pyranocarboxylic acid, is a cyclooxygenase-2 selective inhibitor, and its cutaneous side effects vary from pruritus to severe bullous reactions[3,4].

A 72-year-old female patient was admitted to the hospital with rashes after etodolac use. On dermatological examination, small erythematous plaque on the palate, Nikolsky (+) intact bulla, and partially eroded areas on her neck, trunk, and extremities were observed (Figure 1A-C). Her medical history revealed frequent intake of NSAIDs for dental problems and three episodes of erythematous eruption, which regressed with hyperpigmentation over the past 15 months. She was taking etodolac until she was admitted to us. Her medical history and clinical manifestations led to the diagnosis of GBFDE as she mentioned that each time she used etodolac the lesions recurred at the same body sites. Causality assessment was conducted using the Naranjo adverse drug reaction probability scale, and the score was 6. The adverse reaction was categorized as "probable"[4,5]. She was treated with systemic methylprednisolone and discharged with faded lesions after 3 weeks (Figure 1D-F).

A 76-year-old female patient took etodolac-containing analgesic by mistake and was admitted to the hospital because of bulla formation on her foot and re-inflammation in body sites where she previously had drug reactions (Figure 2). She revealed that on the first episode, she had

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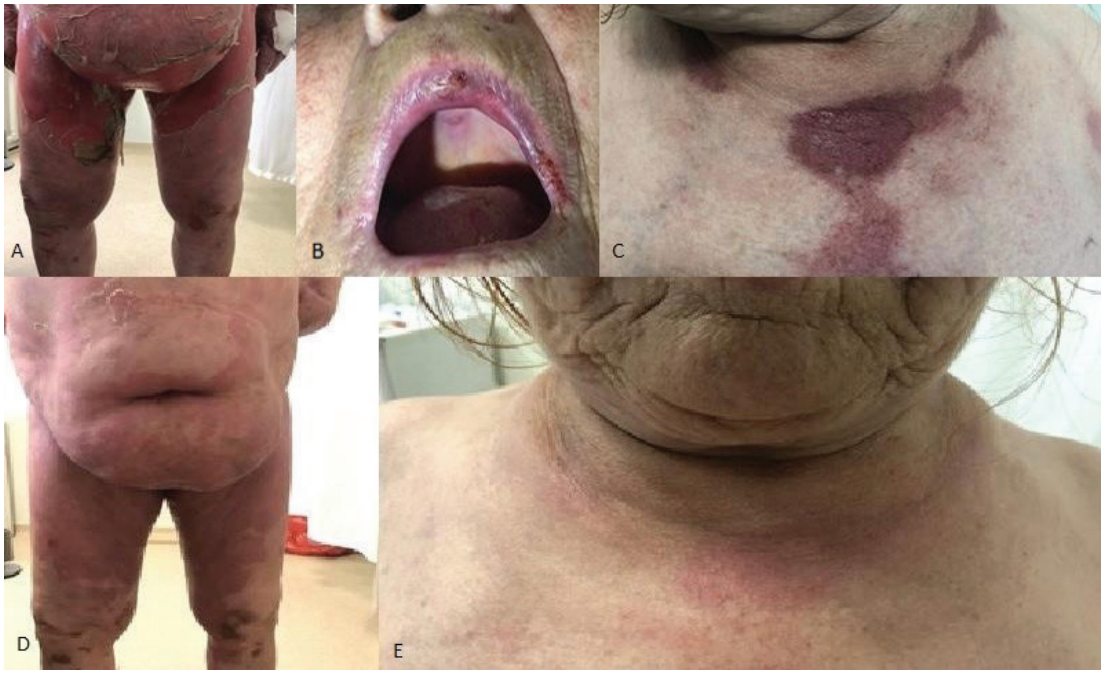

Figure 1. Pretreatment erythematous eroded zones, loose bulla, purplish plaque with typical clear borders on the neck, and eroded plaque on the upper palate (A-C). Lesions regressing after treatment (D, E)

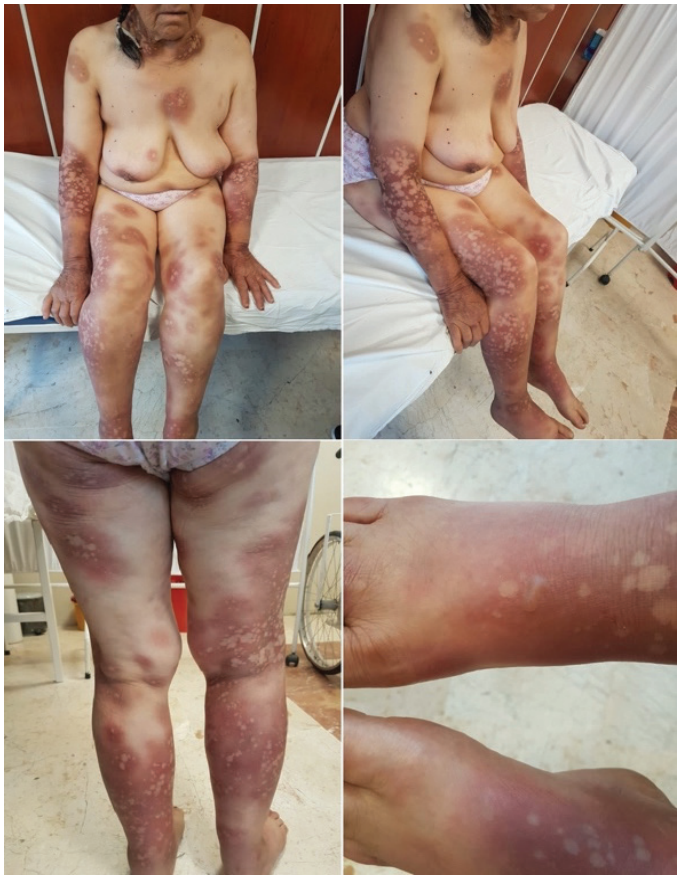

Figure 2. Erythematous purplish plaques in the whole body and postinflammatory hypopigmentation zones instead of the recovered bulla. New bulla generation on the erythematous plaque on foot dorsum

disseminated erythematous-purplish plaques on her entire body surface after taking analgesia seven years ago. The patient was hospitalized 5 years ago because of disseminated bullae formation in addition to erythema following the use of etodolac and ofloxacin-containing drugs. The lesions regressed, leaving hyperpigmentation on erythematous areas and postinflammatory hypopigmentation on the sites of bullae. Histopathological examination demonstrated mild spongiosis, vacuolar interface dermatitis with many necrotic keratinocytes, pigment incontinence, and eosinophil predominant mixed infiltration in the perivascular area of the papillary dermis (Figure 3). The lesions are taken under control through systemic steroids.

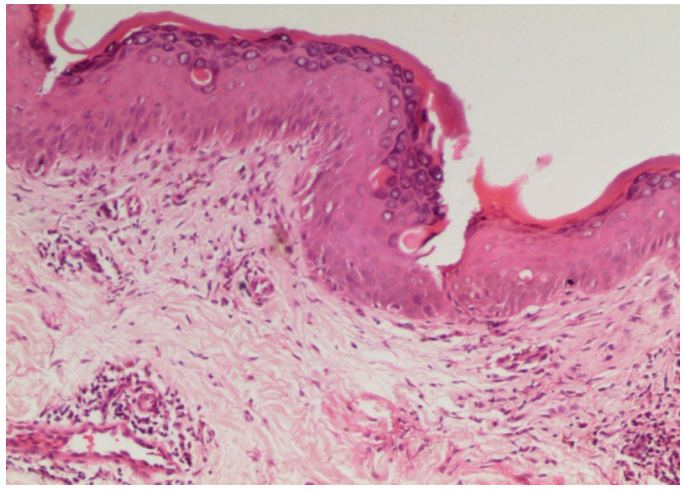

Figure 3. Histopathological examination showing focal parakeratosis, mild spongiosis, vacuolar interface dermatitis with many necrotic keratinocytes, pigment incontinence, and eosinophilic predominant mixed infiltrate more prominant in the perivascular area of the papillary dermis (hematoxylin and eosin staining, x10)

Table 1. Clinical presentation of etodolac-induced fixed-drug eruption cases in the literature

Author	Year	Age-sex	Additional disease	Presentation	Diagnosis
Yeo et al.[6]	1999	37-M	Osteomyelitis, allergic contact dermatitis	Well-demarcated violaceus plaques on the wrist and thigh	Non-pigmented fixed-drug eruption
Ozkaya and Keles[7]	2007	52-F	Osteoarthritis	Oral mucosa erosion and multiple well-demarcated violaceus plaques	Pigmented fixed-drug eruption
Koca Kalkan et al.[8]	2011	30-M	Allergic rhinitis, chronic spontaneous urticaria	Oral mucosa erosion, bullous lesion, and erosions on the lip, penis, and back	GBFDE
Current cases	2023	72-F	Osteoarthritis hypertension	Oral mucosa bulla on the palate and multiple well-demarcated violaceus plaques on the trunk	GBFDE
		76-F	Osteoarthritis diabetes mellitus	Intact bulla on the dorsum of the foot and multiple well-demarcated violaceus plaques on the body	GBFDE

GBFDE: Generalized bullous fixed-drug eruption

When compared with previous attacks, the patient reported intensity of pruritus and shortening of the time interval between drug intake. The Naranjo probability scale score was 7, and the adverse reaction was categorized as "probable."

GFDEs are rarely seen and require differentiation from other blistering diseases. Although FDE generally regresses in days through topical treatment, GBFDE often requires more extensive treatment, with reports controlling skin and mucosa involvement suggesting comparable mortality to SJS/TEN[5]. In diagnosis, lesions recurring in the same regions is specific for FDE and can only be learned through adequate anamnesis. Cho et al.[5] evaluated 23 cases of GBFDE and 11 cases of SJS-TEN and indicated shorter latent interval, less mucosal lesions, more eosinophilic infiltration, and dermal melanophages in the GBFDE group.

FDE is characterized by a drug-induced nonimmediate type IVc reaction. Intraepidermal interferon-producing CD8+ T-cells, possessing a phenotype resembling effector memory T-cells, are found in both resting and acute lesions[7,8]. The interleukin-mediated survival of memory T-cells is responsible for the site-specificity of the lesions. Tissue damage is caused by the intraepidermal clusters of differentiated CD8+ T-cells in the surrounding keratinocytes. FAS/FAS-L, perforin, and granzyme B are expressed in GBFDE, whereas the concentration of granulysin is much lower in GBFDE than in TEN[8].

GBFDE is a rare entity, and a few etodolac-related FDEs and GBFDE cases were reported in the literature[6-8] (Table 1). As a result, etodolac was the probable cause of the adverse reaction based on the Naranjo scale in two GBFDE cases reported here. Patients had self-oral provocation with recurrent uses of the responsible drug.

These cases emphasize the importance of early recognition and removal of causative drugs, their cross-reactants, and preventability of severe clinical presentations and complications by starting suitable treatment promptly.

The patients involved in this report gave written informed consent, authorizing the use and disclosure of their protected health information.

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