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A rare case of generalized bullous fixed drug eruption resembling toxic epidermal necrolysis

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Abstract

Generalized bullous fixed drug eruption (GBFDE) is a rare and severe adverse drug reaction characterized by widespread blisters and erosions involving at least 10% of the body surface. GBFDE can mimic Stevens–Johnson syndrome and toxic epidermal necrolysis (TEN), both clinically and histologically. We present the case of a 76-year-old woman with extensive painful blisters and erosions affecting approximately 70% of her skin, including the oral and genital mucosa, accompanied by an impaired general condition, strongly suggesting TEN. However, the absence of Nikolsky's sign, together with slate-gray hyperpigmentation, pointed toward GBFDE, later supported by histopathological analysis. Paracetamol was identified as the most likely causative agent. Following discontinuation of the culprit drug, the patient was treated with high-dose corticosteroids and antibiotics within a multidisciplinary care approach. After 3 weeks of hospitalization, the skin lesions healed with residual hyperpigmentation, and her condition stabilized. Our case highlights the challenge of differentiating between two uncommon severe disorders with overlapping clinical and histopathological features, including extensive epidermal necrosis and subepidermal blistering. Clinical and pathological correlation by experienced physicians is essential for distinguishing GBFDE from TEN because their management strategies differ, impacting both patient outcomes and healthcare costs.

Keywords: bullous, drug, fixed, reaction, TEN

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Introduction

Generalized bullous fixed drug eruption (GBFDE) is a rare and severe variant of fixed drug eruption (FDE). It presents as widespread blisters and erosions with typical well-demarcated FDE lesions involving at least 10% of the body surface area, distributed on at least three of six different anatomic sites including the head and neck, trunk, extremities, and genitalia (1). Because of the widespread skin lesions, GBFDE can be clinically confused with Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (2–4). In generalized disease, prognosis correlates with the extent of skin detachment (5).

Case report

A 76-year-old Caucasian women presented to the emergency department with a 4-day history of widespread erythema, blisters, and painful erosions on the trunk and extremities (Figs. 1, 2). At the time of presentation, about 70% of the skin was covered with flaccid blisters and erosions with about 15% of the skin detached. In addition, the patient also had genital and oral erosions, with crusting of the lips, as well as conjunctivitis, and she was feeling generally ill. The eruption of skin lesions was followed by malaise and fever (38 °C).

The patient had arterial hypertension, depression, and vertigo, and she had been taking the following medications regularly for several years without any changes in her regimen: amlodipine, ramipril, acetylsalicylic acid, pentaerythrityl tetranitrate, clomipramine, and betahistine, with occasional use of paracetamol for headache. Based on her history, the most suspicious drug was paracetamol.

A detailed medical history revealed that the patient had previously experienced two episodes of FDE, initially presenting as dusky erythematous macules and blisters on the shins. These episodes were mild and localized, and unfortunately they remained unrecognized at the local medical center. She continued to take paracetamol occasionally, which subsequently led to dissemination of the lesions upon re-exposure to the culprit drug.

At admission, the clinical appearance greatly resembled TEN due to widespread erosions and detached skin, but Nikolsky's sign was negative. A shave biopsy of the skin was performed for frozen section analysis. Histopathological findings in cryosections showed subepidermal blistering (Fig. 3). Confluent apoptotic keratinocytes and focal basal vacuolar damage were present in the epidermis, and eosinophils and melanophages with sparse lymphocytic infiltrate were noted in the dermis (Fig. 4). Based on these findings, a diagnosis of fixed drug eruption was made.

Paracetamol was the most suspicious drug and was immediately discontinued, and the patient's cardiological and neurological medications were also replaced with drugs of a different chemical structure. A multidisciplinary approach was required, and so a team of medical specialists including a dermatologist, psychiatrist, cardiologist, and ophthalmologist was included.

Upon admission, laboratory values revealed elevated inflammatory markers, including C-reactive protein mg/l and erythrocyte sedimentation rate (44 mm/h). The patient had mild anemia (hemoglobin 117 g/l, erythrocytes 3.81×10^{12}/l), mild hypoproteinemia (total protein 59 g/l), and slightly reduced albumin (29 g/l). Electrolyte analysis showed mild hypernatremia and hypochloremia. Other laboratory parameters, including urea, creatinine, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, and pancreatic

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enzymes, were within the reference range. Urinalysis was unremarkable. Shortly after the culprit drug was discontinued and systemic corticosteroid and antibiotic therapy was initiated, the initially high inflammation parameters started to decrease. The patient's general condition remained stable most of the time. Anemia, low protein and albumin levels, and electrolyte imbalance also improved after adequate supportive therapy. Although the inflammation was settling and the patient was receiving low molecular weight heparin (LMWH) in prophylactic doses, the D-dimer value was rising (from 1 mg/l to 6.6 mg/l), and color doppler ultrasound of the lower extremities revealed bilateral deep vein thrombosis in the popliteal veins. Therefore, treatment with LMWH in therapeutic doses was continued.

After 3 weeks of hospital care—with her general condition stabilized, widespread erosions healed, and secondary infections treated—the patient was discharged with residual hyperpigmented macules on the skin (Fig. 5).

Discussion

Although FDE is a common adverse drug reaction caused by over 100 different medications with a characteristic clinical presentation, there are also rarer forms that can pose a diagnostic challenge, such as non-pigmented, linear, and even vesiculobullous forms (6). One of the rarest, but possible, clinical presentations of FDE is GBFDE or TEN-like FDE, which is considered the most severe form of FDE (7).

Cases of GBFDE imitating TEN have previously been described (8–10), with diclofenac, ceftriaxone, ibuprofen, and trimethoprim/sulfamethoxazole marked as the most likely culprit agents. There have also been a few reported cases of GBFDE occurring after the influenza vaccine (11, 12), which implies the necessity of taking a detailed history of all medications and vaccinations.

A retrospective study of 18 cases with GBFDE from Tunisia showed that bullous fixed drug eruptions could also be easily misdiagnosed as other bullous dermatoses, such as pemphigus, bullous pemphigoid, erythema multiforme major, SJS, or TEN (13), which can lead to inappropriate treatment. To adequately treat GBDFE and patients with TEN, it is essential to differentiate between these two conditions; this is not always easy, but it can be guided by clinical and histological parameters.

Regarding clinical features, a study by Cho et al. suggested that patients with GBFDE had shorter latent periods and less mucosal involvement than patients with TEN (1). It was shown that GBFDE had a more rapid onset, developing within 1 to 24 hours, rather than within weeks, as in TEN. In addition, GBFDE had less or no mucosal and systemic involvement, and a tendency for a more favorable prognosis. However, recent experience suggests it may be equally as life threatening as TEN (14).

The main differential diagnoses in our case were also GBFDE and TEN because the medical history implicated a drug as the suspected agent, with the extensive erosions and impaired general condition strongly suggesting a diagnosis of TEN. In our case, skin changes also appeared quickly after taking the drug, but the erosions were extensive and even affected the mucous membranes. All of this, combined with the patient's poor general condition, even complicated with popliteal thrombosis, led us to suspect TEN. However, the negative Nikolsky's sign and slate-gray hyperpigmentation pointed toward a diagnosis of GBFDE, later supported by histopathological analysis. Therefore, these two diagnoses should always be considered as differential possibilities.



Figure 1 | Widespread blisters and erosions, as well as hyperpigmented macules on the face, trunk, and extremities. Crusting of the lips suggests involvement of the oral mucosa.



Figure 2 | Widespread, painful blisters and erosions on the back and buttocks.

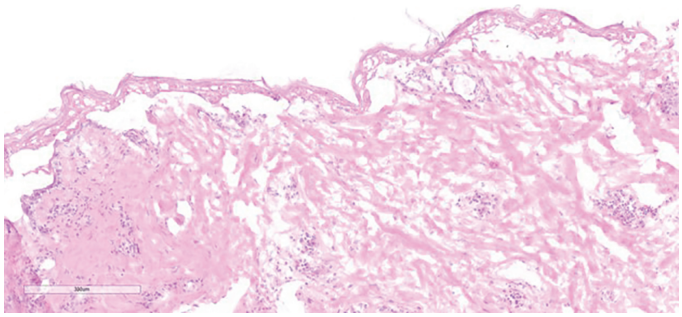


Figure 3 | Subepidermal blistering in skin biopsy (frozen section, hematoxylin-eosin stain, ×200).

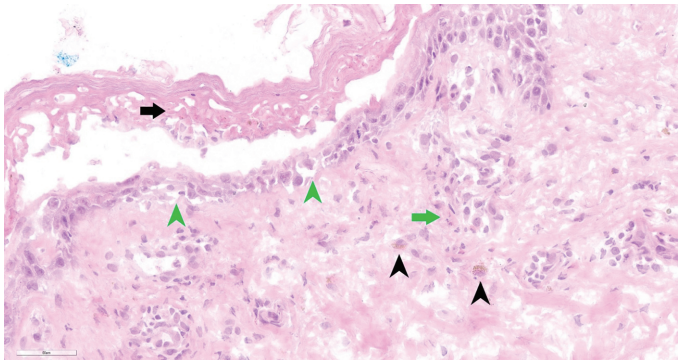


Figure 4 | Confluent apoptotic keratinocytes (black arrow) and basal vacuolar damage (green arrowheads) in the epidermis and eosinophils (green arrow) and melanophages (black arrowheads) in the dermis in skin biopsy (frozen section hematoxylin-eosin stain, ×200).

The histopathological features of GBFDE and TEN overlap. Blistering is a result of vacuolar degeneration of basal keratinocytes and apoptosis of keratinocytes, which are often single or grouped in GBFDE (1, 15). Apoptosis may be extensive and affect the entire epidermis, and it does not favor TEN over GBFDE (16, 17). The presence of eosinophils and melanophages in the dermis favors GBFDE over TEN (15, 16), but for precise differentiation of GBFDE from TEN clinicopathological correlation is crucial. Immunohistochemical staining is not a common practice for differentiating these two entities, although it has been suggested that GBFDE has a greater number of $CD4^+$ and $Foxp3^+$ T cells in the dermis and a smaller number of $CD56^+$ cells in the epidermis compared to TEN (1). To exclude other autoimmune bullous dermatoses, a direct immunofluorescence test should be performed.

Another important diagnostic test is the oral provocation test, which remains the gold standard for identifying the causative drug, but it is not advised in FDE due to the risk of triggering widespread FDE or GBFDE (18). The drug patch test (PT) can help confirm the causative drug in FDE. If performed, PT should be conducted on previously affected (lesional) skin, with unaffected skin serving as a control. The reactivity rates for PT in FDE are variable and are influenced by factors such as the activity of resident $CD8^+$ T cells and absorption of the drug through the skin. However, some experts discourage its use in generalized forms due to the potential risks and limited reliability. Overall, PT is a useful method for identifying the causative drug, particularly in cases of localized FDE involving nonsteroidal anti-inflammatory drugs or multiple drugs, but it should be applied with caution in GBFDE due to potential risks and variable reliability. Its reliability may be limited for certain drug classes, such as antibiotics and allopurinol (19, 20).



Figure 5 | Residual hyperpigmented macules.

Appropriate differentiation of GBFDE from SJS/TEN leads to cost reduction, avoiding the unnecessary use of high doses of systemic corticosteroids, intravenous immunoglobulin, plasmapheresis, cyclosporine, and other immunosuppressive drugs. Identification and discontinuation of the culprit drug remains the most important treatment measure for GBFDE, but in severe and especially generalized bullous cases the short-term use of low doses of corticosteroids may be indicated (20).

Prophylaxis consists of careful drug admission, avoidance of unnecessary medications, and inappropriate use of a large number of medications, especially the most common causative drugs and cross-reacting substances. Special attention should be given to chemically related drugs and possible cross-sensitivity (21).

Conclusions

GBFDE can easily be misdiagnosed as TEN. To accurately differentiate between the two and establish the correct diagnosis, precise anamnestic data, especially regarding all prescribed medications and supplements, along with a thorough clinical examination and histopathological analysis, are essential. Ultimately, the clinicopathological correlation of experienced physicians is crucial in distinguishing GBFDE from TEN.

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