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# Generalized bullous fixed drug eruption treated with cyclosporine

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## Abstract

Fixed drug eruptions (FDE) comprise 10 percent of all adverse cutaneous drug reactions and generalized bullous fixed drug eruptions (GBFDE) are a rare subset of FDEs. We present a patient with severe GBFDE caused by ibuprofen successfully treated with cyclosporine. Further work is needed to determine if cyclosporine can be an effective therapy for GBFDE.

*Keywords: generalized, bullous, fixed drug eruption, treatment, cyclosporine*

## Introduction

Fixed drug eruptions (FDE) comprise 10 percent of all adverse cutaneous drug reactions, and generalized bullous fixed drug eruptions (GBFDE) are a rare subset of FDEs [1]. Fixed drug eruption is a reaction to an offending agent with lesions occurring in the same areas of skin each time the offending drug is taken. The lesions can be single or multiple plaques and appear red to violaceous in color, often leaving post-inflammatory hyperpigmentation following resolution. The most common areas of involvement include the lips, hands, feet, and genitals. Generalized bullous fixed drug eruptions are a specific subtype of fixed drug eruptions in which there is widespread blistering present in addition to the characteristic plaques of fixed drug eruption. Owing to the extensive involvement of multiple sites of the body and the nature of the lesions in which there is skin detachment, generalized bullous fixed drug warrants urgent attention and treatment.

## Case Synopsis

A man in his 40s, with a history of asthma, presented to the emergency department with a painful, generalized eruption that began six days prior. The eruption started 24 hours after he had taken dextromethorphan- guaifenesin and ibuprofen for a cough. He recalled previous milder, localized lesions in some of the same areas several years prior after taking ibuprofen. Physical exam revealed numerous erythematous to violaceous oval macules with dusky centers, coalescing into confluent patches involving the periorbital area, neck, back, and extremities (**Figure 1**). Flaccid bullae were present and most prominent on the upper arms. The lesions were Nikolsky positive. The estimated Nikolsky positive body surface area was 16 percent. Conjunctiva were spared and the upper and lower vermilion lip had small erosions with no intra-oral ulcers noted. Diffuse erosions were present on the glans and distal shaft of the penis.

A punch biopsy was obtained from the upper back. Microscopy revealed focal interface dermatitis consisting mostly of lymphocytes, histiocytes, and rare eosinophils with numerous melanophages, many of which were deep in the mid-dermis. Scattered individually necrotic keratinocytes were also present. Necrotic epidermis was noted beneath a basket-weave cornified layer (**Figure 2**). These findings were consistent with a fixed drug eruption. Given the severity of the eruption, the patient was started on intravenous cyclosporine 3mg/kg in two divided doses. Within 48 hours of treatment, all lesions improved. There was reduction of erythema and pain; the dusky centers failed to progress.

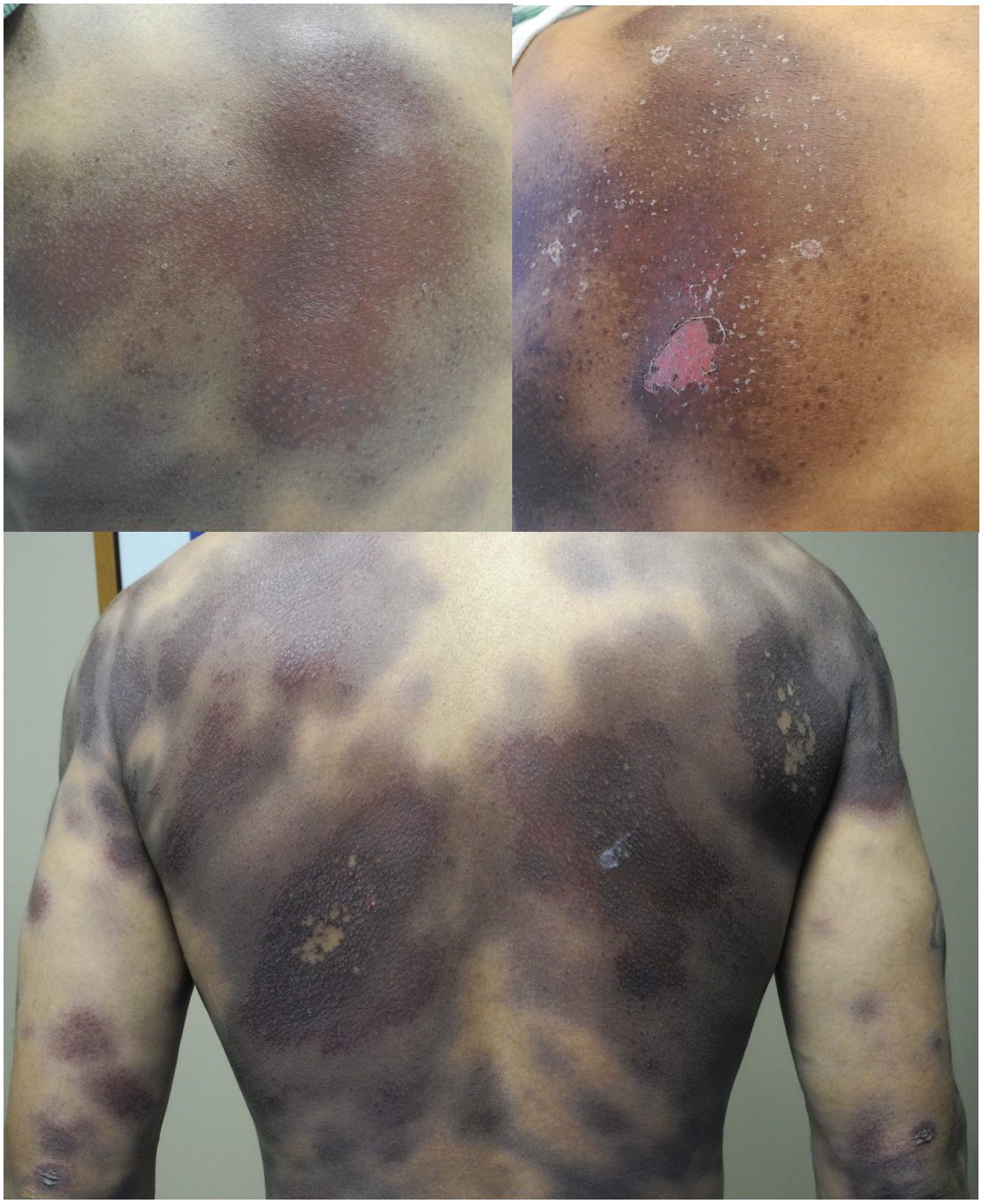

**Figure 1.** *Top image (left) shows baseline eruption with diffuse erythematous to violaceous oval macules and patches with dusky centers at presentation. Top image (right) shows erythema before treatment with cyclosporine and bottom image shows cessation of erythema after treatment with cyclosporine.*

Intravenous cyclosporine was continued for a total of 5 days. Two weeks after discharge, the patient's eruption had resolved and only hyperpigmentation at prior sites was evident.

## Case Discussion

GBFDE is often misdiagnosed as Stevens Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN). When matched for the percentage of Nikolsky positive body surface, GBFDE was found to have a nearly identical mortality rate to SJS/TEN. Therefore, severe cases of GBFDE should be regarded with the same level of urgency as cases of SJS/TEN and the necessity of offering an effective treatment is paramount [2]. Distinguishing GBFDE from SJS/TEN can be difficult. However, several key differences can aid in diagnosis. GBFDE is characterized by its rapid onset within hours of ingestion of the offending drug, whereas the onset of SJS is typically over 1-3 weeks. There are a few reports of SJS/TEN occurring

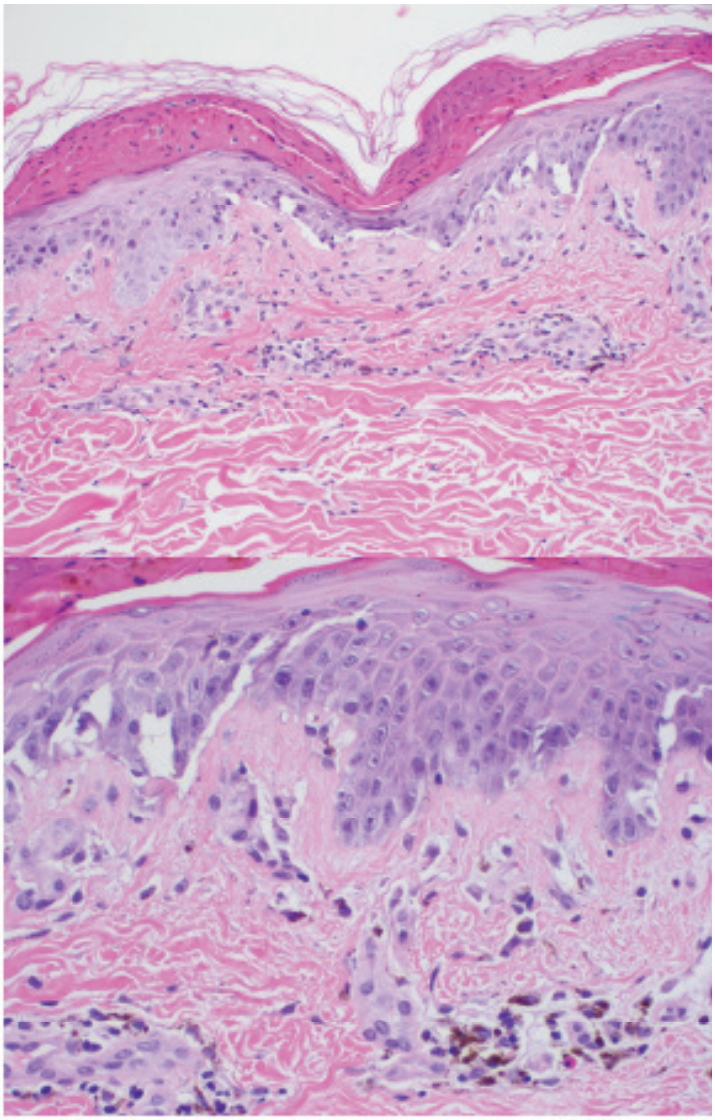

**Figure 2.** *Top image with hematoxylin and eosin staining revealing a necrotic epidermis beneath a basket-weave cornified layer. Bottom image with hematoxylin and eosin staining showing focal residual interface dermatitis with lymphocytes and histiocytes with numerous melanophages, and individual necrotic keratinocytes.*

as early as three days, but this is not typical [2,3]. Patients with GBFDE lesions often note a history of similar lesions in identical locations. The eruption is typically widespread with well-defined round blisters, erosions, and erythematous patches intermixed with typical lesions of non-generalized fixed drug eruption. GBFDE also lacks the small spots and atypical target lesions seen in SJS. Histopathologically, GBFDE has a greater infiltration of lymphocytes and a greater degree of pigment incontinence with the presence of dermal melanophages compared to SJS.

The current management of FDE includes immediate discontinuation of the offending drug, topical antibiotics, emollients, and analgesics for pain control [4]. Currently there is no specific therapy targeted to the treatment of GBFDE. Systemic treatment with corticosteroids and intravenous immunoglobulins (IVIG) is debated and studies thus far are inconclusive.

The mechanism of FDE involves intra-epidermal CD8+ T cells that are present within lesions and play a role in local tissue destruction [5]. Clinically resolved FDE lesions continue to harbor a substantial number of effector memory CD8+ T cells at the dermal-epidermal junction, which allows for recurrence of the lesions in the same location [6]. Based on the pathogenesis of FDEs, we believe that cyclosporine has a superior therapeutic effect over prednisone or IVIG by specifically targeting the activity of T cells. Cyclosporine inhibits dephosphorylation of the nuclear factor of activated T cells (NFAT) leading to decreased IL-2 production. This ultimately leads to diminishment of CD4 and CD8 T-cell responses and T cell-mediated tissue damage.

## Conclusion

We present a case of GBFDE with rapid cessation of erythema and improvement of all lesions after treatment with cyclosporine. This case suggests a potential therapeutic role for cyclosporine in GBFDE especially given the potential high mortality, which warrants further investigation in the future.

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