CASE REPORT

Generalized bullous fixed-drug eruption secondary to the influenza vaccine

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INTRODUCTION

Fixed drug eruption (FDE) is a type IV hypersensitivity reaction characterized by recurrence of lesions at identical sites with each exposure to the offending medication. After morbilliform exanthems, FDE is the most common cutaneous drug reaction.1 Generalized bullous fixed drug eruption (GBFDE) is a variant of FDE that can present rarely with significant, life-threatening body surface involvement akin to Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).2 There are few reported cases of GBFDE occurring after the influenza vaccine, and all occurred after decades of receiving the vaccine.3,4 Here we report a rare case of GBFDE occurring as a result of administration of the influenza vaccine.

CASE REPORT

A 67-year-old African-American woman with type 2 diabetes mellitus, hypertension, chronic obstructive pulmonary disease, and coronary artery disease presented with an exquisitely painful bullous eruption.

Three days after administration of the quadrivalent influenza vaccine, she presented with multiple 2.5- to 5-cm hyperpigmented patches and plaques with a peripheral rim of erythema (Fig 1, A), some with overlying flaccid bullae, located on her bilateral hips and lower back (Fig 1, B). She had a background of numerous hyperpigmented patches coalescing on the back, flanks, and buttocks consistent with postinflammatory hyperpigmentation as a result of a similar bullous eruption after the influenza vaccine 1 year prior.

A thorough medication review failed to find any other recent medication changes. New bullae continued to appear across her groin, lower back, buttocks, axillae, and abdomen over the subsequent days. Although a few oral erosions involving the hard palate and vermilion lips were present, there was no evidence of ocular or genital mucosal involvement. There was complete sparing of the distal extremities including the palms and soles. She remained afebrile with a normal complete blood count and comprehensive metabolic panel.

Biopsy found vacuolar interface dermatitis with subepidermal vesicle formation, epidermal necrosis, marked pigment incontinence, and mild lympho-eosinophilic infiltrate (Fig 1, C). These findings were consistent with the biopsy results from 1 year prior. The episode at that time was of a similar clinical presentation and resolved after 7 days of topical clobetasol 0.05% ointment.

Abbreviations used:
EM: erythema multiforme
FDE: fixed drug eruption
GBFDE: generalized bullous fixed drug eruption
SJS: Stevens-Johnson syndrome
TEN: toxic epidermal necrolysis

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During the second bullous eruption, the patient required use of both topical clobetasol ointment and an oral prednisone taper. Within 2 days of hospitalization, new lesions continued to appear, now covering 15% of her total body surface area. The patient was transferred to the burn intensive care unit for aggressive wound care. She was discharged after 14 days in the burn intensive care unit, with complete resolution at 30 days.

**DISCUSSION**

FDE is characterized by discrete, well-demarcated, violaceous, circular patches or plaques that are typically self-limited. However, a life-

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**Fig 1.** Generalized bullous fixed drug eruption after the influenza vaccine. **A**, Well-demarcated red-brown patches with surrounding rim of erythema in a background of postinflammatory hyperpigmentation. **B**, Numerous coalescing bullae. **C**, Vacuolar interface dermatitis, dyskeratotic keratinocytes with a lympho-eosinophilic infiltrate (arrows). (C, Hematoxylin-eosin stain; original magnification: ×40.)

**Table I.** Clinical factors that favor GBFDE over EM or SJS/TEN

| Primary morphology | Body surface area involvement | Histopathologic features | Features of our patient |
|--------------------|-------------------------------|--------------------------|-------------------------|
| Fixed drug eruption | Well-demarcated red to brown patches or edematous plaques ± bullae with PIH | Variable | Vacular interface dermatitis with lymphoehosinophilic infiltrate and pigment incontinence, ± dyskeratotic keratinocytes | Well-demarcated red-brown patches with overlying bullae and in a background of diffuse PIH; eosinophilic infiltrate on histopathology |
| EM | 3-zone target lesions or atypical papular targets | Acral, initially on extremities, ± 1 mucosal surface | <10% | Lymphocytic vacuolar interface dermatitis, dyskeratosis throughout all layers of epidermis |
| SJS | Atypical macular targets with bullae formation | Trunk and proximal extremities, palms and soles; ≥ 2 mucosal surfaces | <10% | Confluent epidermal necrosis, minimal inflammatory infiltrate |
| TEN | Atypical macular targets with bullae formation | Trunk and proximal extremities, palms and soles; ≥ 2 mucosal surfaces | >30% | Full-thickness epidermal necrosis, minimal inflammatory infiltrate |

PIH, Postinflammatory hyperpigmentation.
threatening form of FDE with numerous coalescing flaccid bullae can develop with repeated exposures.\textsuperscript{1} Our patient’s second influenza vaccination essentially served as a systemic provocation test, which was positive. Here, we present a unique case of GBFDE secondary to the influenza vaccine.

Taken together, our patient’s reproducible bullous eruption and supportive biopsy results after receiving the influenza vaccine were consistent with GBFDE. There are multiple clinical factors that favor GBFDE over erythema multiforme (EM) or SJS/TEN (Table I). The strictly proximal distribution, large size of each primary lesion (2.5–4 cm) distributed over a background of diffuse postinflammatory hyperpigmentation, and rim of erythema are clinical evidence supportive of GBFDE rather than EM. Additionally, the patient only had involvement of one mucosal surface, whereas patients with SJS/TEN typically have more extensive mucosal involvement of 2 or more mucosal sites. Furthermore, the presence of eosinophils on histopathology are suggestive of a drug-induced process such as FDE rather than EM. The delayed onset of her eruption may have been related to intramuscular delivery of the offending drug.

FDE is typically a benign and self-limiting reaction, resolving in days to weeks with topical therapy; however, GBFDE often requires more extensive treatment, with reports controlling for body surface involvement suggesting comparable mortality to SJS/TEN.\textsuperscript{2} Current evidence-based standards of care for management are lacking; however, some successful treatments of GBFDE include immunomodulatory agents such as cyclosporine and prednisone.\textsuperscript{5,6} In our patient, progression despite initiation of oral prednisone warranted transfer to the burn intensive care unit where aggressive support prevented life-threatening fluid losses, electrolyte imbalances, and secondary infections. Further research into the pathophysiology and treatment are needed to reduce the morbidity and mortality of this condition.

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