

UC Davis

Dermatology Online Journal

Title

Generalized bullous fixed drug eruption imitating toxic epidermal necrolysis: a case report and literature review

Permalink

<https://escholarship.org/uc/item/25v009gs>

Journal

Dermatology Online Journal, 23(7)

Authors

Mitre, Victoria
Applebaum, Danielle S
Albahrani, Yasser
et al.

Publication Date

2017

DOI

10.5070/D3237035734

Copyright Information

Copyright 2017 by the author(s). This work is made available under the terms of a Creative Commons Attribution-NonCommercial-NoDerivatives License, available at <https://creativecommons.org/licenses/by-nc-nd/4.0/>

Peer reviewed

Generalized bullous fixed drug eruption imitating toxic epidermal necrolysis: a case report and literature review

Victoria Mitre¹, Danielle S Applebaum¹ MD, Yasser Albahrani² MD, Sylvia Hsu¹ MD

Affiliations:

¹Baylor College of Medicine, Department of Dermatology, Houston, Texas

²University of Texas Southwestern, Department of Dermatology, Dallas, Texas

Corresponding Author: Victoria Mitre, One Baylor Plaza, Baylor College of Medicine, Houston, TX 77030, Email: victoria.mitre@bcm.edu

Abstract

Fixed drug eruption (FDE) is defined as sharply demarcated erythematous patches or plaques that occur secondary to systemic exposure to a causative medication. Eruptions are deemed “fixed” because upon repeated exposure they recur at previously affected sites. Generalized bullous fixed drug eruption (GBFDE) is a rare FDE variant occurring in patients with a previous history of FDE. Given the extensive cutaneous involvement and the frequent mucosal ulcerations associated with GBFDE, it is challenging to discern these lesions from Steven-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). The presence of significantly elevated lesional and serum granulysin in SJS/TEN is an important discriminating factor because granulysin levels remain significantly lower in GBFDE. The implementation of an immunochromatographic test for rapid detection of elevated granulysin levels could therefore facilitate the early diagnosis of SJS/TEN. We report a case of GBFDE to elucidate the characteristic differences in clinical presentation, histopathology, and immunohistochemistry that can facilitate diagnosis.

Keywords: fixed drug eruption, generalized bullous fixed drug eruption, Stevens-Johnson syndrome, toxic epidermal necrolysis

Introduction

Fixed drug eruption (FDE) is defined as sharply demarcated dusky-red, erythematous patches or plaques that recur at the same site secondary to systemic exposure to a causative medication [1-3].

Although spontaneous resolution within 7-10 days after offending agent cessation is the norm, post-inflammatory hyperpigmentation is an enduring remnant of FDE [4]. Repeated exposure to the causative medication tends to increase reaction severity, rarely causing a widespread bullous reaction known as generalized bullous fixed drug eruption (GBFDE), [2]. Generalized bullous fixed drug eruption presents a diagnostic challenge because it has features reminiscent of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), including widespread cutaneous involvement and frequent mucosal ulcerations [5] and generalized bullous fixed drug eruption (GBFDE).

Case Synopsis

A 50-year-old woman presented to the hospital with widespread, painful, blistering lesions that began within 24 hours after treatment with ceftriaxone. She had dialysis-dependent end-stage renal disease, diabetes mellitus, congestive heart failure, systemic lupus erythematosus, and three prior episodes of generalized bullous eruptions over the past 2.5 years; these episodes were diagnosed once as a cutaneous lupus flare and twice as TEN.

With each episode, she presented with numerous painful, irregular, dusky, erythematous to violaceous patches and thin plaques, many of which had overlying flaccid, yet intact, bullae. The lesions were scattered throughout her trunk and upper and lower extremities, with less involvement of her face and neck (**Figure 1**). In addition, she had significant oral mucosal ulceration and stomatitis with crusting of the lips.



Figure 1. *Hyperpigmented, dusky patches, some with bullae.*

At initial presentation 2.5 years earlier, histopathologic examination revealed an interface dermatitis with a subepidermal blister and scattered necrotic keratinocytes. Direct immunofluorescence (DIF) favored a mixed connective tissue disease and she was diagnosed with a cutaneous lupus flare. She experienced a recurrence 1.5 years later and was diagnosed clinically with TEN; pathologic examination was not performed at that time. When the lesions recurred 6 months later, histology showed full-thickness epidermal necrosis, necrotic keratinocytes, and a subepidermal blister; DIF was negative. She was again diagnosed with TEN.

During the most recent admission, the clinical presentation was nearly identical to the preceding episodes, with > 50% body surface area involvement and > 30% skin detachment. Two repeat biopsies revealed interface dermatitis with lymphocytic predominance, numerous melanophages, and scattered individual necrotic keratinocytes consistent with a diagnosis of fixed drug eruption (**Figures 2, 3**). DIF was again negative.

Although the patient was on a multitude of medications during each episode, including several

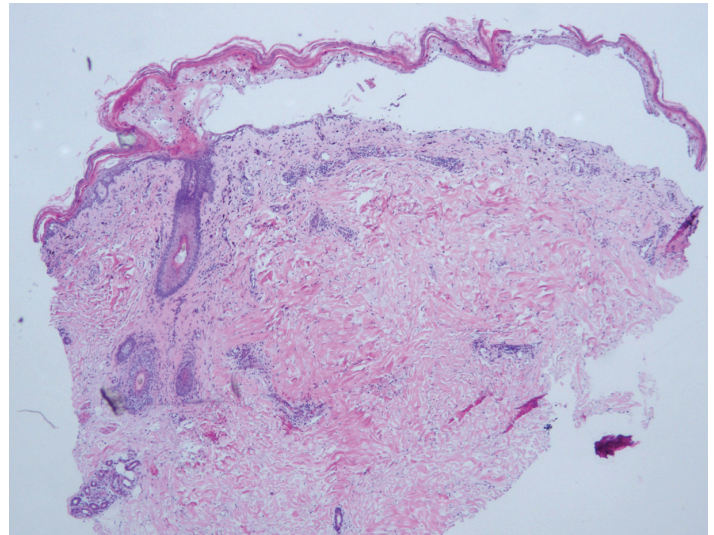


Figure 2. *Subepidermal clefting with interface dermatitis and epidermal necrosis (H&E, 40x).*

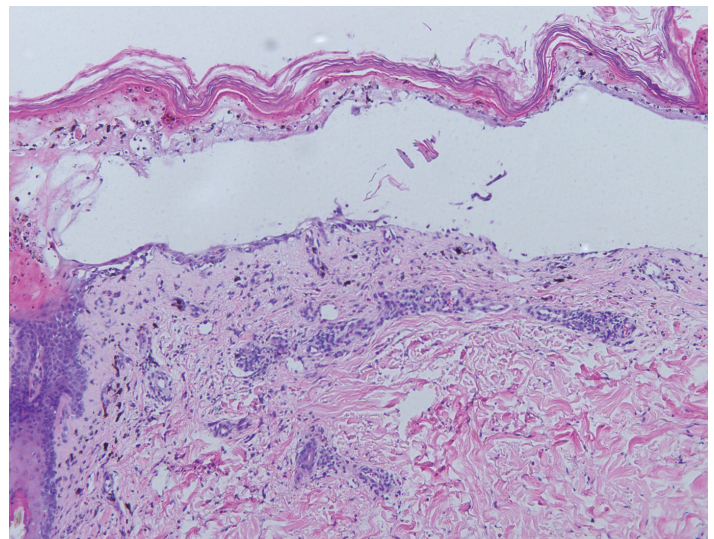


Figure 3. *Normal basketweave stratum corneum with epidermal vesiculation, necrotic keratinocytes, dermal fibrosis and pigmentary incontinence (H&E, 100x).*

antibiotics, extensive chart review revealed exposure to a cephalosporin antibiotic within the 24 hours preceding onset of each eruption. After prompt antibiotic termination and supportive treatment, the lesions markedly improved.

Case Discussion

Drug eruptions are among the most frequently encountered dermatologic complaints, arising in approximately 2-3% of clinical inpatients [1, 6]. The most common offending medications include nonsteroidal anti-inflammatory drugs, antimicrobials, and antiepileptics; the incidence associated with any particular medication varies geographically and

historically owing to the frequency of its use [1-3, 5, 7]. Fixed drug eruption is characterized as a delayed-type hypersensitivity reaction occurring secondary to systemic exposure to a causative medication [8]. Lesions are “fixed” meaning that upon repeated exposure they recur at the previously affected site, but may occur with increased severity [1, 2]. Although the pathogenesis remains unclear, it is hypothesized that FDE results from activation of intraepidermal CD8+ T cells, which cause direct cytolysis of surrounding keratinocytes and release numerous destructive cytokines into the local environment [8].

Generalized bullous fixed drug eruption is a rare variant of FDE that characteristically presents with generalized bullae and erosions accompanying the distinctive FDE lesions with involvement of at least three of the following anatomic sites: head and neck (including lips), anterior or posterior trunk, upper limbs, lower limbs, and genitalia [5, 9]. The eruptions are separated by large regions of intact skin and a majority of patients experience <10% skin detachment [10]. The differential diagnosis of GBFDE invariably includes SJS and TEN [4, 9].

Medical history and clinical presentation are critical to differentiating GBFDE from SJS/TEN. The timing from exposure to the medication to the onset of cutaneous findings can provide a clue for diagnosis; FDE generally occurs within 30 minutes to 24 hours of exposure whereas drug exposure can precede SJS/TEN by 1 to 3 weeks [7]. Furthermore, a history of recurrent lesions at the same sites is pathognomonic for FDE. A Taiwanese study by Lee et al. found that a history of previous events was reported in 67% of GBFDE cases, but was absent in patients with SJS/TEN [5] and generalized bullous fixed drug eruption (GBFDE). Constitutional symptoms (fevers, chills, or malaise) are seen in 50% of patients with SJS/TEN but only 11% of patients with GBFDE [5] and generalized bullous fixed drug eruption (GBFDE). Mucous membrane involvement has been reported in only 44-67% of patients with GBFDE but is found in all patients with SJS/TEN [5, 9]. Although GBFDE reportedly has a better prognosis than SJS/TEN, a recent study reported that GBFDE had only slightly lower mortality rates than SJS/TEN (22% for GBFDE versus 28% for SJS/TEN), [4, 10].

Vacuolar interface dermatitis is the most common histopathologic pattern shared among all drug eruptions [11]. Characteristic histopathologic features of GBFDE include individual apoptotic keratinocytes scattered throughout the epidermis, prominent dermal eosinophilic and lymphocytic infiltration, and dermal melanophages. In contrast to FDE, SJS/TEN exhibits clusters of apoptotic keratinocytes, often with full-thickness epidermal necrosis, and fewer eosinophils and dermal melanophages [5, 9].

Immunohistochemistry of GBFDE reveals a greater extent of dermal CD4+ and Foxp3+ cell infiltration, and fewer intraepidermal CD56+ and granulysin+ cells compared to patients with SJS/TEN. Granulysin is a cytotoxic molecule known to cause rapid extensive epidermal necrosis [9, 12]. It has been shown to be distinctly elevated in the early stages of SJS/TEN, while maintaining significantly lower serum levels in GBFDE patients [9, 12]. For this reason, serum granulysin levels could be used as a marker for differentiating GBFDE from SJS/TEN in cases of diagnostic uncertainty. Fujita et al. developed a 15-minute immunochromatographic test for detecting high granulysin levels with a sensitivity of 80% and a specificity of 96% for SJS/TEN versus other drug eruptions [12]. There are multiple alternatives for measuring serum granulysin levels, but the rapid immunochromatographic granulysin test could facilitate an early diagnosis of SJS/TEN without requiring a laboratory.

The mainstay therapeutic management of both GBFDE and SJS/TEN is mostly supportive after causative medication cessation [1]. In patients with drug eruptions and numerous new medications, an extensive chart review may reveal prior episodes, easing the identification of the culprit agent. If the clinical history remains equivocal, patch testing at a previously involved site can detect the medication in approximately 33% of cases [5, 7]. Although systemic provocation testing is the most reliable method for diagnosis, it is contraindicated in both conditions [1, 13]. Although the skin lesions of FDE resolve within 7-10 days after terminating the medication, they often heal with post-inflammatory hyperpigmentation [4, 13]. Supportive treatment with analgesics, emollients, corticosteroids, and antibiotics may be needed to promote healing and prevent infection [4, 13].

Conclusion

Our report suggests that definitive diagnosis of GBFDE requires an indicative clinical history and confirmatory histopathologic and immunohistochemical analysis. Furthermore, serum granulysin levels are markedly elevated in the early stages of SJS/TEN but remain low in GBFDE. Although not yet commercially available, the widespread employment of a rapid immunochromatographic test could expedite the diagnosis of SJS/TEN. Identification of the causative agent allows for prompt cessation of the medicine thereby reducing morbidity and mortality and decreasing the risk of future exposures.

References

1. Lee AY. Fixed drug eruptions. Incidence, recognition, and avoidance. *Am J Clin Dermatol*. 2000 Sep-Oct;1(5):277-85. [PMID:11702319].
2. Jung J-W, Cho S-H, Kim K-H, Min K-U, Kang H-R. Clinical Features of Fixed Drug Eruption at a Tertiary Hospital in Korea. *Allergy Asthma Immunol Res*. 2014 Sep;6(5):415-20. [PMID: 25228998].
3. Kavoussi H, Rezaei M, Derakhshandeh K, Moradi A, Ebrahimi A, Rashidian H, et al. Clinical Features and Drug Characteristics of Patients with Generalized Fixed Drug Eruption in the West of Iran. *Dermatol Res Pract*. 2015;2015:236703. [PMID: 26783389].
4. Dharamsi FM, Michener MD, Dharamsi JW. Bullous Fixed Drug Eruption Masquerading as Recurrent Stevens Johnson Syndrome. *J Emerg Med*. 2015 May;48(5):551-4. [PMID: 25433836].
5. Lee C-H, Chen Y-C, Cho Y-T, Chang C-Y, Chu C-Y. Fixed-drug eruption: A retrospective study in a single referral center in northern Taiwan. *Dermatol Sin*. 2012 Mar;30(1):11-15.
6. Arndt KA, Jick H. Rates of cutaneous reactions to drugs. A report from the Boston Collaborative Drug Surveillance Program. *JAMA*. 1976 Mar 1;235(9):918-23. [PMID: 128641].
7. Patell RD, Dosi RV, Shah PC, Joshi HS. Widespread bullous fixed drug eruption. *BMJ Case Rep*. 2014 Feb 7;2014. [PMID: 24510691].
8. Shiohara T. Fixed drug eruption: pathogenesis and diagnostic tests. *Curr Opin Allergy Clin Immunol*. 2009 Aug;9(4):316-21. [PMID: 19474709].
9. Cho Y-T, Lin J-W, Chen Y-C, Chang C-Y, Hsiao C-H, Chung W-H, et al. Generalized bullous fixed drug eruption is distinct from Stevens-Johnson syndrome/toxic epidermal necrolysis by immunohistopathological features. *J Am Acad Dermatol*. 2014 Mar;70(3):539-48. [PMID: 24388722].
10. Lipowicz S, Sekula P, Ingen-Housz-Oro S, Liss Y, Sassolas B, Dunant A, et al. Prognosis of generalized bullous fixed drug eruption: comparison with Stevens-Johnson syndrome and toxic epidermal necrolysis. *Br J Dermatol*. 2013 Apr;168(4):726-32. [PMID:23413807].
11. Meyers W, Metze, D. Histopathology of drug eruptions - general criteria, common patterns, and differential diagnosis. *Dermatol Pract Concept*. 2011 Jan; 1(1): 33-47. [PMID: 24396718].
12. Fujita Y, Yoshioka N, Abe R, Murata J, Hoshina D, Mae H, et al. Rapid immunochromatographic test for serum granulysin is useful for the prediction of Stevens-Johnson syndrome and toxic epidermal necrolysis. *J Am Acad Dermatol*. 2011 Jul;65(1):65-8. [PMID: 21507517].
13. Flowers H, Brodell R, Brents M, Wyatt JP. Fixed Drug Eruptions: Presentation, Diagnosis, and Management. *South Med J*. 2014 Nov;107(11):724-7. [PMID: 25365443].