Volume 24 Number 4| April 2018| 24(4): 14

Generalized fixed drug eruption to piperacillin/tazobactam and review of literature

Heather Kornmehl[1] BS, Farzam Gorouhi[2] MD, Thomas Konia[2] MD, Maxwell A Fung[2] MD, Danielle M Tartar[2] MD PhD

Affiliations: [1]Drexel University College of Medicine, Philadelphia, Pennsylvania, USA, [2]University of California Davis, Sacramento, California, USA

Corresponding Author: Danielle M Tartar MD, PhD, University of California, Davis, 3301 C Street, Suite 1400, Sacramento, CA 95816, Email: DTartar@ucdavis.edu

Abstract

Fixed drug eruption (FDE) is an adverse drug reaction characterized by the development of well-circumscribed, round, dusky erythematous macules and plaques on cutaneous or mucosal surfaces. The reaction occurs on the same mucosal or cutaneous site with subsequent exposures to the offending drug. Although FDE usually manifests as a single lesion, in rare instances, more than one lesion may arise and this is referred to as a generalized eruption. Herein, we present a 31year-old man with history of cystic fibrosis who developed a generalized fixed drug eruption to piperacillin/tazobactam (Zosyn, Pfizer). We discuss our patient's course and review causes and outcomes of *generalized* fixed drug eruptions in the literature.

Keywords: fixed drug eruption, generalized fixed drug eruption, piperacillin/tazobactam

Introduction

Fixed drug eruption (FDE) is an adverse drug reaction characterized by the development of well-circumscribed, round, dusky erythematous macules and plaques on cutaneous or mucosal surfaces [1-5]. This reaction is often accompanied by a sensation of burning or pruritus and occurs in the same mucosal or cutaneous site with each subsequent exposure to the offending agent [1, 2]. Although the exact pathophysiology has not been elucidated, CD8+ T cells are believed to play a role in causing the epidermal damage [1, 2, 6]. Although FDE usually manifests as a single lesion, in rare instances more than one lesion may arise, which is referred to as a generalized eruption [2-4]. Although FDE to piperacillin/tazobactam has been reported in the literature [7], herein we report a case of *generalized* FDE to piperacillin/tazobactam and review reported causes of generalized FDE in the literature.

Case Synopsis

A 31-year-old man with a past medical history of patent foramen ovale, cystic fibrosis, diabetes mellitus type II, and pancreatic insufficiency was admitted for a cystic fibrosis flare. The patient received piperacillin/tazobactam and developed several non-pruritic dusky, grey two-toned macules and patches <3cm in size on the hands, arms, legs, and abdomen (**Figure 1**). The patient reported that when he was previously treated with piperacillin/tazobactam two months prior, he developed a similar solitary asymptomatic patch on his dorsal hand, which was persistent at the time of presentation. Biopsy from the dorsal hand revealed junctional vacuolar alteration and necrotic keratinocytes along the dermal-epidermal junction and superficial, predominantly lymphocytic infiltrates with sparse eosinophils and neutrophils. The presence of melanophages around superficial vessels supported the clinical impression of a fixed drug reaction (**Figure 2**). The offending medication

A

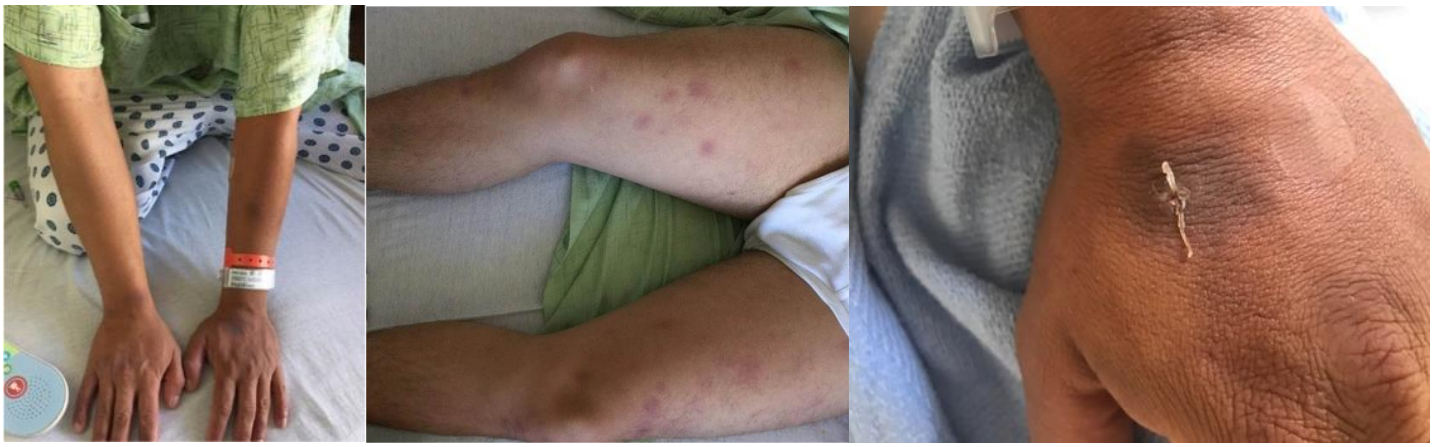

Figure 1. *Generalized Fixed Drug Eruption:* ***A)****,* ***B)*** *distribution of the dusky lesions on the upper and lower extremities, respectively.* ***C)*** *Shows the biopsy site of the primary lesion on the left dorsal hand*

was continued and the patient was treated with triamcinolone 0.1% ointment with improvement.

Discussion

Although antibiotics are one of the most common culprits of FDE, to our knowledge, this is the first known case of *generalized* FDE to piperacillin/tazobactam in the literature. Generalized FDE comprise only a small subset of FDE [2]; we therefore set out to review cases of generalized FDE is in the literature, the agents implicated, and the timing of the drug eruptions (**Table 1**). We conducted a PubMed search using the term "generalized fixed drug eruption" spanning January 2001 though November 2017. Only case reports and case-control studies written in English were eligible for inclusion. Our search yielded 27 articles containing 45 cases [1-28]. Three articles were excluded because one was not written in English [26] and two were not case reports or case-control studies [15, 17].

Our findings from this review correlate with information concerning FDE elsewhere in the literature. NSAIDS and antibiotics are two of the most common types of pharmacologic agents implicated

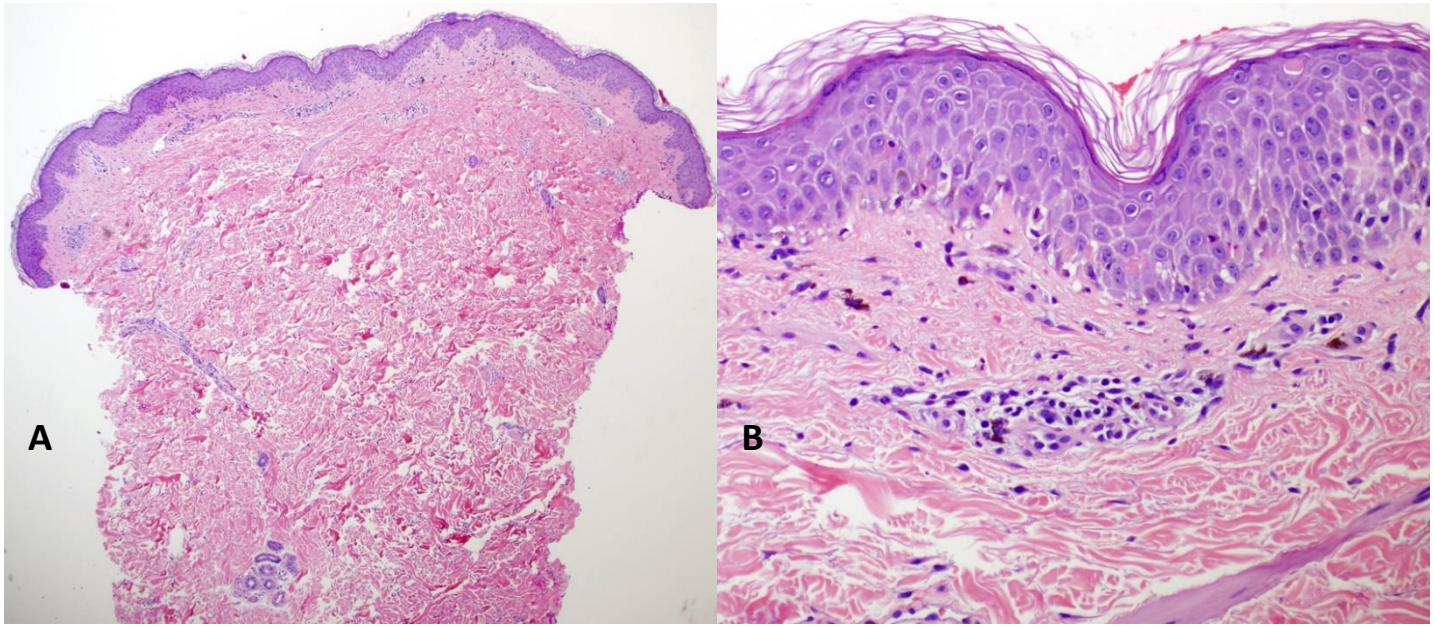

Figure 2. *Histpathologic findings of fixed drug eruption. Biopsy findings include a vacuolar interface dermatitis and melanin pigment around superficial vessels, supporting the impression of a generalized fixed drug eruption. H&E,* ***A)*** *4×,* ***B)*** *20×.*

in FDE [3, 5, 6, 29]. This was also the case for our review of generalized FDE in which 22 (50%) of the cases implicated antibiotics [4-6, 10, 12, 13, 20, 21, 28], and 16 (36%) implicated NSAIDS [1-3, 9, 11, 14, 16, 20, 25]. FDE tends to occur within 30 minutes to 24 hours after exposure [29]. Most of the generalized FDE cases included in our review also occurred within this interval [2-6, 8-10, 12-14, 16, 21, 23-25]. Additionally, it has been noted that the number of sites affected may increase with re-exposure to a given drug, meaning an FDE can present as generalized FDE upon re-exposure [3, 6, 29]. This correlates with our patient's account and several cases in our review [1-3, 9, 10, 12, 18, 21, 23, 28].

In the majority of cases in our review, the offending drug was discontinued [1, 4-6, 9, 11, 13, 14, 16, 18, 21-25, 27, 28]. In our patient's case, piperacillin/tazobactam was considered critical for his long-term prophylactic management, so this medication was continued. The patient was treated with triamcinolone 0.1% ointment with improvement.

Conclusion

Although there are many reported cases of FDE in the literature, there are few cases of generalized FDE [2]. To help address this gap, we describe the first reported case to our knowledge of a patient who developed a generalized FDE to piperacillin/tazobactam.

Table 1. *Reported Cases of Generalized Fixed Drug Eruption.*

Source Article (year) [Reference]	Offending drug	Timing of eruption after drug initiation	Was the drug stopped?
Garcia- Doval et al. (2001) [8]	Influenza Vaccine	12-24 hours	Not applicable
Leivo et al. (2004) [9]	Naproxen	Within 24 hours	Yes
Ada et al. (2008) [10]	Ciprofloxacin	"a few hours"	Yes
Bandino et al. (2009) [11]	Naproxen	Not stated	Yes
Hager et al. (2009) [12]	Levofloxacin & Ciprofloxacin	12 hours	Not stated
Rho et al. (2010) [1]	Piroxicam	48 hours	Yes
Sawada et al. (2011) [13]	Pazufloxacin	1 hour	Yes
Bilgili et al. (2012) [2]	Diclofenac potassium	6 hours	Not stated
	Naproxen	2 hours	Not stated
Chen & Chiang (2012) [14]	Ibuprofen	6 hours	Yes
Nitya et al. (2013) [5]	Doxycycline	Within 24 hours	Yes
Rubegni et al. (2013) [16]	Nimesulide	12 hours	Yes
Balta et al. (2014) [3]	Flurbiprofen	6 hours	Not stated
Can et al. (2014) [6]	Trimethoprim/Sulfamethoxazole	30 minutes- 1 hour	Yes
Kaku et al. (2014) [18]	Tranexamic acid	Not stated	Yes
Ozkol et al. (2014) [19]	Ursodeoxycholic acid	5 days	Not stated
Kavoussi et al. (2015) [20]	Cotrimoxazole (6)* Metronidazole (4)* Ibuprofen (3)* Doxycycline (2)* Nitrofurantoin Azithromycin Mefenamic acid Meloxicam Novafen	Not stated	Not stated
Kim et al. (2015) [4]	Cefaclor	Within 24 hours	Yes
Podder et al. (2016) [21]	Doxycycline	Within 24 hours	Yes
Vide et al. (2016) [22]	Bromhexine	Not stated	Yes
Garcia & Cohen (2017)[28]	Dapsone	Not stated	Yes
Fukuda et al. (2017) [23]	Pseudoephedrine hydrochloride	6 hours	Yes
Georgesen et al. (2017) [24]	Mycophenolate	Within 24 hours	Yes
Malviya et al. (2017) [25]	Ibuprofen	24 hours	Yes
Ramirez-Bellver et al. (2017) **[27]**	Metformin	Not stated	Yes

References

1. Rho YK, Yoo KH, Kim BJ, Kim MN, Song KY. A case of generalized fixed drug eruption due to a piroxicam plaster. *Clin Exp Dermatol.* 2010;35(2):204-5. [PMID: 20447085].
2. Bilgili SG, Calka O, Karadag AS, Akdeniz N, Kosem M. Nonsteroidal anti-inflammatory drugs-induced generalized fixed drug eruption: two cases. *Hum Exp Toxicol.* 2012;31(2):197-200. [PMID: 21677025].
3. Balta I, Simsek H, Simsek GG. Flurbiprofen-induced generalized bullous fixed drug eruption. *Hum Exp Toxicol.* 2014;33(1):106-8. [PMID: 23703815].
4. Kim EJ, Kim JE, Ro YS, Ko JY. Cefaclor-Induced Generalized Fixed Drug Eruption. *Ann Dermatol.* 2015;27(4):465-6. [PMID: 26273172].
5. Nitya S, Deepa K, Mangaiarkkarasi A, Karthikeyan K. Doxycycline induced generalized bullous fixed drug eruption - A case report. *J Young Pharm.* 2013;5(4):195-6. [PMID: 24563602].
6. Can C, Akkelle E, Bay B, Arican O, Yalcin O, Yazicioglu M. Generalized fixed drug eruption in a child due to trimethoprim/sulfamethoxazole. *Pediatr Allergy Immunol.* 2014;25(4):413-5. [PMID: 24750132].
7. Santosa A, Teo BW, Shek LP. Fixed drug eruption caused by piperacillin-tazobactam. *J Investig Allergol Clin Immunol.* 2013;23(2):132-3. Epub 2013/05/10. [PMID: 23654084].
8. Garcia-Doval I, Roson E, Feal C, De la Torre C, Rodriguez T, Cruces MJ. Generalized bullous fixed drug eruption after influenza vaccination, simulating bullous pemphigoid. *Acta Derm Venereol.* 2001;81(6):450-1. [PMID: 11859962].
9. Leivo T, Heikkila H. Naproxen-induced generalized bullous fixed drug eruption. *Br J Dermatol.* 2004;151(1):232. [PMID: 15270899].
10. Ada S, Yilmaz S. Ciprofloxacin-induced generalized bullous fixed drug eruption. *Indian J Dermatol Venereol Leprol.* 2008;74(5):511-2. [PMID: 19052425].
11. Bandino JP, Wohltmann WE, Bray DW, Hoover AZ. Naproxen-induced generalized bullous fixed drug eruption. *Dermatol Online J.* 2009;15(11):4. [PMID: 19951640].
12. Hager JL, Mir MR, Hsu S. Fluoroquinolone-induced generalized fixed drug eruption. *Dermatol Online J.* 2009;15(12):8. [PMID: 20040258].
13. Sawada Y, Nakamura M, Tokura Y. Generalized fixed drug eruption caused by pazufloxacin. *Acta Derm Venereol.* 2011;91(5):600-1. [PMID: 21597677].
14. Chen JF, Chiang CP. Dermacase. Can you identify this condition? Generalized fixed drug eruption. *Can Fam Physician.* 2012;58(6):659-61. [PMID: 22700734].
15. Lipowicz S, Sekula P, Ingen-Housz-Oro S, Liss Y, Sassolas B, Dunant A, Roujeau JC, Mockenhaupt M. Prognosis of generalized bullous fixed drug eruption: comparison with Stevens-Johnson syndrome and toxic epidermal necrolysis. *Br J Dermatol.* 2013;168(4):726-32. [PMID: 23413807].
16. Rubegni P, Tognetti L, Tosi GM, Flori ML, Fimiani M. Ocular involvement in generalized fixed drug eruption from nimesulide. *Clin Exp Ophthalmol.* 2013;41(9):896-8. [PMID: 23448657].
17. Cho YT, Lin JW, Chen YC, Chang CY, Hsiao CH, Chung WH, Chu CY. Generalized bullous fixed drug eruption is distinct from Stevens-Johnson syndrome/toxic epidermal necrolysis by immunohistopathological features. *J Am Acad Dermatol.* 2014;70(3):539-48. [PMID: 24388722].
18. Kaku Y, Ito T, Kudo K, Kido-Nakahara M, Nakahara T, Moroi Y, Furue M. Generalized fixed drug eruption induced by tranexamic acid. *Eur J Dermatol.* 2014;24(3):408-9. [PMID: 24876162].
19. Ozkol HU, Calka O, Dulger AC, Bulut G. Ursodeoxycholic acid induced generalized fixed drug eruption. *Cutan Ocul Toxicol.* 2014;33(3):256-8. [PMID: 24147950].
20. Kavoussi H, Rezaei M, Derakhshandeh K, Moradi A, Ebrahimi A, Rashidian H, Kavoussi R. Clinical Features and Drug Characteristics of Patients with Generalized Fixed Drug Eruption in the West of Iran (2005-2014). *Dermatol Res Pract.* 2015;2015:236703. [PMID: 26783389].
21. Podder I, Chandra S, Das A, Gharami RC. Doxycycline Induced Generalized Bullous Fixed Drug Eruption. *Indian J Dermatol.* 2016;61(1):128. [PMID: 26955169].
22. Vide J, Moreira C, Cunha AP, Baldaia H, Magina S, Azevedo F. Generalized Bullous Fixed Drug Eruption due to Bromhexine. *Dermatol Online J.* 2016;22(7). [PMID: 27617726].
23. Fukuda R, Ouchi T, Hirai I, Funakoshi T, Honda A, Tanese K, Tanikawa A, Amagai M, Takahashi H. Non-pigmenting fixed drug eruption with mixed features of acute generalized exanthematous pustulosis induced by pseudoephedrine: a case report. *Contact Dermatitis.* 2017;77(2):123-6. [PMID: 28703347].
24. Georgesen C, Lieber S, Lee H. A generalized fixed drug eruption associated with mycophenolate. *JAAD Case Rep.* 2017;3(2):98-9. [PMID: 28361108].
25. Malviya N, Cyrus N, Vandergriff T, Mauskar M. Generalized bullous fixed drug eruption treated with cyclosporine. *Dermatol Online J.* 2017;23(2). [PMID: 28329494].
26. Paulmann M, Mockenhaupt M. [Unintended rechallenge: Generalized bullous fixed drug eruption in two elderly women]. *Hautarzt.* 2017;68(1):59-63. [PMID: 27448063].
27. Ramirez-Bellver JL, Lopez J, Macias E, Fuertes L, Andres I, Alegria V, Gimeno I, Perez A, Perez Y, Requena L. Metformin-Induced Generalized Fixed Drug Eruption With Cutaneous Hemophagocytosis. *Am J Dermatopathol.* 2017;39(6):471-5. [PMID: 27906695].
28. Garcia D, Cohen PR. Dapsone-associated fixed drug eruption. *Expert Rev Clin Pharmacol.* 2017;10(7):717-25. Epub 2017/04/25. [PMID: 28434260].
29. Pai VV, Bhandari P, Kikkeri NN, Athanikar SB, Sori T. Fixed drug eruption to fluconazole: a case report and review of literature. *Indian J Pharmacol.* 2012;44(5):643-5. Epub 2012/11/01. [PMID: 23112430].