

Fixed Drug Eruptions: A Case Report and Review of the Literature

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The estimated time to complete this activity is 1 hour.

GOAL

To understand fixed drug eruption (FDE) to better manage patients with the condition

LEARNING OBJECTIVES

Upon completion of this activity, you will be able to:

1. Describe the clinical presentation of FDEs including nonpigmenting and generalized bullous FDEs.
2. Name the medications most commonly associated with FDEs.
3. Outline methods to determine the causative medication, including topical and oral provocation testing.

INTENDED AUDIENCE

This CME activity is designed for dermatologists and general practitioners.

CME Test and Instructions on page 221.

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Fixed drug eruptions (FDEs) have been described since 1889 with continually evolving documentation of implicated agents and clinical presentations. We report a case of FDE as a reaction to

naproxen sodium in a 27-year-old woman. We offer an inventory of common causes of FDEs as well as a discussion of the spectrum of clinical presentations and differential diagnoses for this peculiar drug reaction.

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Fixed drug eruption (FDE) was first described by Bourns¹ in 1889 and has long been clinically described as a sudden eruption of round to oval, edematous, dusky red macules or patches on

the skin and mucous membranes that leave residual hyperpigmentation, most commonly as a reaction to orally ingested drugs or drug components.² Recent research has provided histologic and immunologic insight into the natural course and pathophysiology of the disease.³ With the advent of a multitude of new medications and preservatives within medications, physicians are seeing both typical and unusual presentations of FDEs often mimicking dermatologic entities such as erythema multiforme,⁴ Stevens-Johnson syndrome,⁵ toxic epidermal necrolysis (TEN),^{5,6} cellulitis,⁷ paronychia,⁷ and bullous pemphigoid.^{8,9} We aim to provide a comprehensive review of FDEs and their implicated offenders.

Case Report

A 27-year-old woman presented to our dermatology clinic with an erythematous patch over her right popliteal fossa that had recurred over 2 years and was transient (Figure). She first noticed the lesion during the first trimester of pregnancy with her third child. With the exception of intermittent use of pain relievers early on, she reported taking only prenatal vitamins and denied using over-the-counter medications. Over the ensuing years, the lesion erupted quickly multiple times without a prodrome and resolved in 3 to 4 days with residual postinflammatory hyperpigmentation (PIH). When present, the lesion was erythematous and pruritic. She previously had used pimecrolimus cream 1% for atopic dermatitis without clinical improvement. Her medical history included atopic dermatitis and von Willebrand disease. She reported taking ibuprofen for relief of menstrual symptoms with occasional use of naproxen sodium if



A 27-year-old woman with a recurrent hyperpigmented 5-cm patch with a 2- to 3-mm erythematous border over the right popliteal fossa.

ibuprofen was unavailable. At presentation she had a hyperpigmented 5-cm patch with a 2- to 3-mm erythematous border that appeared 24 hours prior. After careful review of the patient's medical history and both prescription and over-the-counter medication regimens as well as physical examination, the patient was diagnosed with an FDE in response to naproxen sodium. She was instructed to avoid this medication indefinitely and has not had any recurrences. Rechallenge with ibuprofen proved uneventful and the residual PIH completely faded without intervention.

Comment

Fixed drug eruption is a unique form of drug allergy that characteristically occurs in the same site(s) with each administration of the inciting drug. After initial use of the offending agent, a variable refractory period of weeks, months, or years may pass before the lesions first appear on the skin of a sensitized individual.² With repeated exposure to the agent, either via oral or topical administration, acute lesions typically develop within 30 minutes to 8 hours and present as single or multiple, round, sharply demarcated, dusky red macules, patches, or plaques that may be pruritic and edematous.^{10,11} Pruritus and burning may be the only manifestations of reactivation in a PIH lesion.¹² Initial lesions typically are solitary, but with repeated ingestion of the offending drug, new lesions may appear and original lesions may increase in size. Lesions may blister and erode, leaving residual and persistent pigmentation changes, especially in patients with darker skin phototypes (ie, Fitzpatrick skin types IV to VI). However, blister formation and erosion are not necessary to produce the hallmark PIH changes. Clinically, a PIH lesion may be the only remnant between attacks. A refractory phase may occur following an acute flare in which exposure to the offending drug will not exacerbate the lesion for weeks to months.¹³ The most common cause of FDE (of any type) is trimethoprim-sulfamethoxazole.¹⁴

Nonpigmenting FDE was first described in 1987 by Shelley and Shelley¹⁵ and is characterized by large, symmetric, well-circumscribed, tender, erythematous plaques, occasionally with large bullae over involved areas,^{3,15-20} that suddenly appear but fade over 2 to 3 weeks without the residual PIH characteristically seen in the more common FDEs.² Diagnosis is confirmed in these cases by appearance of the lesion at the exact location of prior eruptions. Pseudoephedrine hydrochloride is the most common instigator of this particular eruption.²¹ It also has been seen following influenza vaccination and has been mistakenly diagnosed initially as bullous pemphigoid.^{8,9}

Generalized bullous FDEs, characterized by multiple, sharply defined, deep red macules distributed

Additional Causes of Fixed Drug Eruptions^{2,3,7-9,14-20,23,24,27,28}

Antibacterial and Antiviral Agents	Psychoactive Agents	Anti-inflammatory Agents (continued)	Miscellaneous
Acyclovir	Barbiturates ^a	Ibuprofen	Allopurinol
Amoxicillin	Carbamazepine	Indomethacin	Articaine
Ampicillin	Chloral hydrate	Mefenamic acid ^a	Atenolol
Chlorhexidine gluconate	Chlordiazepoxide hydrochloride	Metamizole sodium	Botulinum toxin
Clarithromycin	Chlormezanone	Naproxen sodium	Cimetidine ^b
Clindamycin	Citicoline	Nimesulide	Colchicine
Fluoroquinolones	Codeine	Oxyphenbutazone	Contrast media ^b
Foscarnet sodium	Lamotrigine	Phenacetin	Cyproterone acetate
<i>p</i> -Aminosalicylic acid	Lormetazepam	Phenazone ^a	Docetaxel
Penicillin	Ondansetron hydrochloride	Phenylbutazone ^a	Melatonin
Antiparasitic Agents	Opium alkaloids	Piroxicam ^a	Omeprazole
Albendazole	Belladonna	Quinine sulfate	Oral contraceptives
Pyrantel pamoate	Papaverine	Tolfenamic acid	Pamabrom
Tinidazole	Oxazepam	Antihistamines	Phenolphthalein
Antifungal Agents	Phenytoin	Cetirizine hydrochloride	Procarbazine
Azole antifungals	Prochlorperazine maleate	Cyclizine	Tartrazine
Clioquinol	Tropisetron	Diphenhydramine hydrochloride	Tetrahydrozoline ^b
Griseofulvin	Anti-inflammatory Agents	Hydroxyzine hydrochloride	Ticlopidine hydrochloride
Terbinafine hydrochloride	Acetaminophen ^a	Loratadine	
	Aspirin	Orphenadrine	
	Celecoxib	Decongestants	
	Diclofenac sodium	Amlexanox	
	Diflunisal	Citrolone	
	Dipyrrone		
	Ethenzamide		

^aKnown causes of generalized bullous fixed drug eruptions.²³

^bKnown causes of nonpigmenting fixed drug eruptions.^{3,8,9,15-20}

bilaterally and often symmetrically^{2,3,22} may mimic erythema multiforme,⁴ Stevens-Johnson syndrome,⁵ and TEN.^{5,6} These lesions display vesicles and bullae of varying sizes, and the lesions tend to increase in size days after the offending drug has been discontinued. Implicated agents include aminophenazone, antipyrine, barbiturates, clotrimoxazole, trimethoprim, sulfamethoxazole, diazepam, mefenamic acid, acetaminophen, phenazone, phenylbutazone, piroxicam, sulfadiazine, and sulfathiazole.²³ Milder forms of bullous FDE involving 1 to 10 bullous lesions are more commonly seen than generalized bullous FDE, and implicated agents include rifampicin, metronidazole, paracetamol, paclitaxel, vinbucrine, erythromycin, and ibuprofen.²

Fixed drug eruptions commonly have been seen on the oral mucous membrane, glans penis, lips, genitals, perineal area, and tongue. These lesions present abruptly and manifest clinically as bullous lesions or erosions, with or without involvement of other areas of the skin.² Specific subtypes include glans penis FDE, which often is caused by tetracycline hydrochloride or sulfonamides and clinically presents as balanitis in an uncircumcised penis. Eruption on the lips typically is associated with naproxen sodium and oxycams, and eruption on the genitals (male and female involvement) typically is associated with clotrimazole ingestion.^{2,24}

Other less common presentations include FDE of a distal phalanx that may mimic acute paronychia. Erythematous and edematous plaques with undermined borders have been initially diagnosed as cellulitis; however, recurrence after administration of the offending drug confirmed them as FDE.⁷

Fixed drug eruptions of any type may occur anywhere on the skin, but common locations include the lips, palms, soles, glans penis, and groin area.³ Most FDE lesions occur after ingestion of the offending drug rather than injection or topical application. Notably, FDEs have been reported postcoitally in patients with a sexual partner who had ingested the offending agent.^{25,26} The average age of presentation is 31.3 years for females and 30.4 years for males (age range, 1.5–87 years).²⁷ Other frequently implicated drugs are listed in the Table.

Histologic examination of biopsy specimens taken 1 to 2 days following onset of the lesion have demonstrated hydropic degeneration of basal keratinocytes resulting in pigment incontinence and associated lymphocytic invasion of the epidermis predominantly involving the interfollicular epidermis. The upper dermis is edematous and contains mixed infiltrates of lymphocytes, neutrophils, histiocytes, mast cells, and eosinophils. It also may contain a large amount of melanin and melanin-laden macrophages.^{2,3,24}

Immunohistochemical studies demonstrate large numbers of CD3⁺CD8⁺ T cells aligned along the epidermal side of the dermoepidermal junction.³ The epidermis demonstrates a predominant infiltrate of CD8⁺ T cells, whereas CD4⁺ T cells permeate the perivascular and interstitial dermis. CD8⁺ T cells residing in FDE lesions in both active and resting states are suggested to be the key players in mediating local epidermal injury associated with FDEs.³ It is thought that the activated CD8⁺ T cells produce interferon- γ and may interact directly with other inflammatory cells, thereby initiating a cascade of events resulting in epidermal injury.³

Identification of the offending drug can be assessed by both systemic and topical (ie, patch test) provocation tests. Oral provocation may lead to generalized bullous lesions in some cases.²⁹ Topical provocation is the safest diagnostic tool and the gold standard for identifying cross-reacting and nonreacting compounds related to the offending drug.²⁸ When the drug in question contains several ingredients, all components must be suspected and tested separately.² A low concentration is applied to the skin, distant from the possible FDE site. If a reaction is not noted, a gradual increase in the drug concentration is applied until the full therapeutic dose is achieved. The appearance of erythema, edema, and vesicles in association with pruritus or burning is indicative of a positive provocation test result. Oral provocation tests should be administered only when results of topical tests at full dosage are negative and a strong suspicion of FDE to the drug in question remains.²⁸ When conducting a patch test of a suspicious drug, application at a site far from the reaction site will cause an FDE at the former reaction site, not at the test site itself.³⁰

Therapy for FDE is challenging. Topical steroids and oral antihistamines can be attempted to control symptoms but typically have little if any effect. Hydroquinone bleaching creams can be used to try and reduce any persistent PIH. Avoidance of the offending agent is the most useful treatment.³⁰

Conclusion

Fixed drug eruptions have been well described in the literature, but with the development of a multitude of new medications, a wide spectrum of FDEs have been seen that may mimic other more emergent dermatologic entities. We encourage physicians to consider FDEs, specifically nonpigmenting, bullous, and generalized bullous FDEs, when evaluating patients for erythema multiforme, Stevens-Johnson syndrome, TEN, cellulitis, and bullous pemphigoid.

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