Foresee Your Next Patient

Fixed Drug Eruption

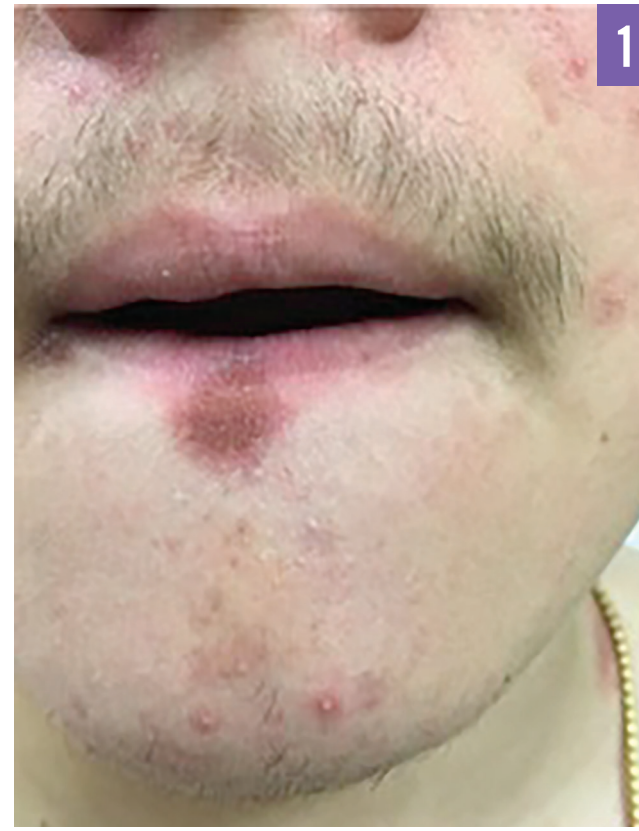
Emma Basaran, MD[1] • Samantha Bartling, DO[2]

A 16-year-old boy with a history of insulin-dependent type 1 diabetes presented to a dermatology clinic with a 1-year history of nonpruritic erythematous lesions that had acutely worsened over the past several weeks.

History. His initial skin changes had begun as a single erythematous macule on his left upper arm that had increased in size, then had crusted over before turning light pink in color. The lesion had never completely resolved and had persisted as a light pink round patch until several weeks prior to presentation, during which time the lesion had become dark and tender to the touch. He also had developed numerous new lesions on his lip, chest, and back.

Medication history revealed a new escitalopram prescription 6 months prior to presentation, and the patient reported having taken several over-the-counter cold medications, including products containing pseudoephedrine, several days before the rash had begun to worsen. He also noted a history of occasional over-the-counter cold medication as needed. The patient was otherwise well and denied any systemic symptoms. He also did not report a personal or family history of atopy or drug reactions.

Physical examination. A physical examination revealed Fitzpatrick skin type 3 with multiple discrete lesions. His face had crusted erythematous plaques on the bilateral medial canthi and an additional 6-mm dark red to violaceous macule with surrounding erythema just inferior to his lower cutaneous lip (**Figure 1**). His abdomen, chest, and back had multiple scattered 0.5- to 5.0-cm light pink to dark red macules and patches. A 5-cm dark red to violaceous patch with several central hypopigmented papules and minimal surrounding erythema was present on the upper arm (**Figure 2**). There was also a 15-mm dark red patch along the right deltopectoral groove on the superior chest with surrounding erythema (**Figure 3**).



A 6-mm dark red to violaceous macule with surrounding erythema just inferior to the patient's lower cutaneous lip.

Diagnostic tests. Two punch biopsies were performed, one from the initial lesion on the left upper arm and one from the newest lesion (2 days old) on the right superior chest. Histologic evaluation of both specimens revealed superficial confluent epidermal necrosis with an intact stratum corneum. There was epidermal dysmaturation with reactive atypia and vacuolar alteration with superficial perivascular lymphocytic infiltrate. Few eosinophils were identified, with rare apoptotic keratinocytes in

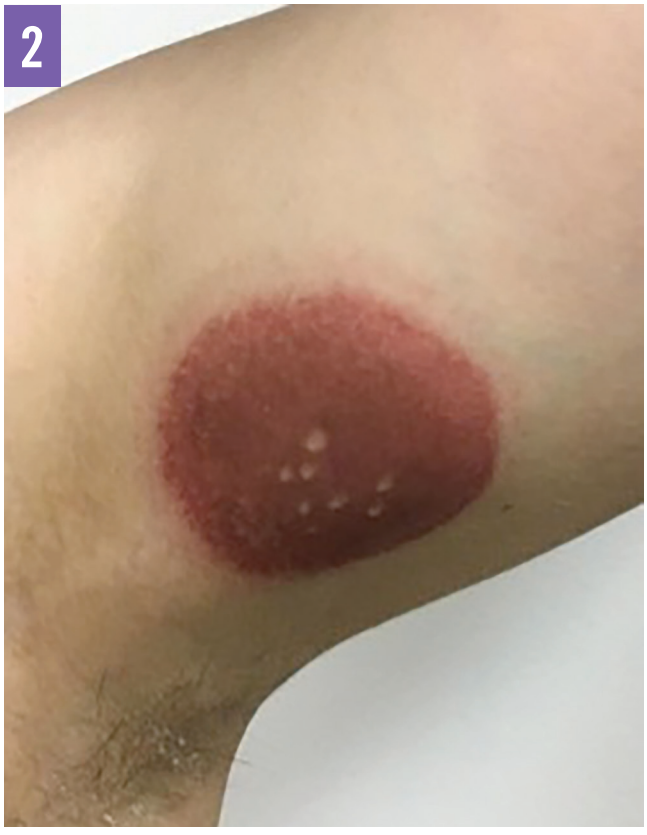
AFFILIATIONS:
[1]Naval Medical Center San Diego, California
[2]Walter Reed National Military Medical Center, Bethesda, Maryland

CITATION:
Basaran E, Bartling S. Fixed drug eruption. *Consultant.* Published online October 15, 2020. doi:10.25270/con.2020.10.00023
Received May 22, 2020. Accepted September 2, 2020.

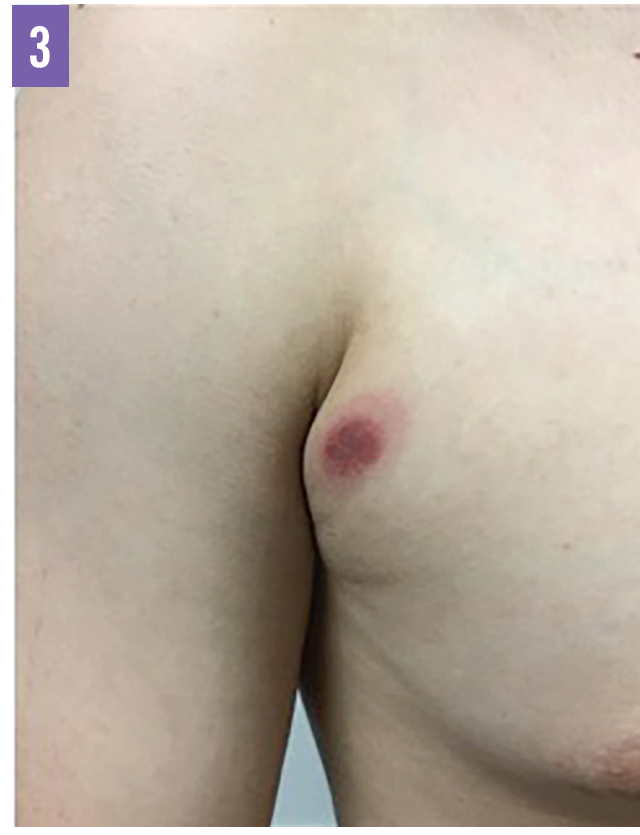
DISCLOSURES:
The authors report no relevant financial relationships.

DISCLAIMER:
The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, the Department of Defense, or the US Government.

CORRESPONDENCE:
Emma Basaran, MD, Naval Medical Center San Diego, 34800 Bob Wilson Dr, San Diego, CA 92134 (emma.f.basaran.mil@mail.mil)



A 5-cm dark red to violaceous patch with several central hypopigmented papules and minimal surrounding erythema on the patient's upper arm.



A 15-mm dark red patch along the right deltopectoral groove on the superior chest with surrounding erythema.

the lower epidermis. These findings were consistent with an interface dermatitis, which although not specific for fixed drug eruption (FDE), are consistent with histological findings in FDE lesions.

Based on biopsy results, clinical findings on examination, and a reported history of worsening lesions following pseudoephedrine ingestion, a presumptive diagnosis of FDE due to pseudoephedrine was made.

Discussion. FDE refers to the development of one or more round or oval, sharply demarcated, erythematous plaques following exposure to a systemic drug. When they initially appear, the plaques may have a violaceous hue or develop bullae leading to erosion but then typically fade into gray-brown hyperpigmented patches. Plaques may occur anywhere on the body, although the most common sites are the lips, face, hands, feet, and genitals. The onset is typically within a few days to 2 weeks after initial exposure to the drug, but with subsequent exposures, the lesions present within 24 hours in the same location. Reactivated lesions often present with a violaceous center surrounded by a concentric erythematous ring,[1] as seen on the right superior chest of our patient. With repeated exposures, the lesions may increase in size or number.

Orally administered medications more commonly result in FDE compared with parenterally administered medications. The most common medications associated with FDE include pseudoephedrine (as in our patient), trimethoprim, tetracycline, barbiturates, sulfonamides, mefenamic acid, acetylsalicylic acid, phenolphthalein, ibuprofen, and oxyphenbutazone. Systemic manifestations, including fever, nausea, arthralgia and malaise, are usually absent with solitary FDE but can be present when multiple lesions arise.[1]

Although FDEs typically resolve with postinflammatory hyperpigmented patches, there have been reports of FDEs that resolve without any pigmentary changes. This nonpigmenting form of FDE has been most commonly associated with pseudoephedrine.[2]

FDE is believed to result from an immunologic response in the skin. Shiohara[3] identified local resident intraepidermal $CD8^+$ T cells with effector-memory phenotype as playing a key role in the pathophysiology, triggering localized tissue damage.

Additional recruitment of $CD4^+$ and $CD8^+$ T cells is believed to assist in the destruction of keratinocytes and the release of cytokines. After the destruction, the cytotoxic T cells remain in the epidermis and release more cytokines upon reexposure to the offending agent, which explains the reappearance of FDEs in the same location after reexposure to the drug.[3]

Management and treatment. FDE has a benign clinical course and outcome. Identification and cessation of the causative medication is essential to prevent repeated episodes. Symptomatic management with systemic antihistamines or topical corticosteroids may be all that is required for acute eruptions. If lesions evolve and become more bullous-appearing, it is important to consider toxic epidermal necrolysis (TEN) and autoimmune blistering diseases. Direct immunofluorescence can be helpful in identifying autoimmune bullous disease, although it will be negative in the case of TEN.[1]

Identifying the causative drug is important to prevent reactivation or future lesions but can be difficult in the setting of multiple medications. Andrade and colleagues[1] conducted a 20-year review to evaluate the utility of patch testing in identifying the drug culprit for FDE in the clinical setting, since oral challenges can often result in severe reactions or induce new lesions. Patch testing appears to be a safe and effective method of testing for FDE patches related to nonsteroidal anti-inflammatory drugs; however, it may be of limited utility for antibiotics, antihistamines, and allopurinol.[4] Positive patch test results for pseudoephedrine-induced FDE lesions is even more limited.[5] Nonlesional skin patch testing (ie, in areas unaffected by the suspected FDE) were negative in nearly all patients and should not be used in identifying the cause of an individual's FDE.[4] Rather, a thorough review of a patient's medication list and identification of common FDE-associated drugs should be performed, with elimination or substitution of possible causative agents as is medically appropriate. ■

REFERENCES:

1. Hoetzenecker W, Nägeli M, Mehra ET, et al. Adverse cutaneous drug eruptions: current understanding. *Semin Immunopathol.* 2016;38(1):75-86. doi:10.1007/s00281-015-0540-2
2. Vidal C, Prieto A, Pérez-Carral C, Armisén M. Nonpigmenting fixed drug eruption due to pseudoephedrine. *Ann Allergy Asthma Immunol.* 1998; 80(4):309-310. doi:10.1016/S1081-1206(10)62974-2
3. Shiohara T. Fixed drug eruption: pathogenesis and diagnostic tests. *Curr Opin Allergy Clin Immunol.* 2009;9(4):316-321. doi:10.1097/ACI.0b013e32832cda4c
4. Andrade P, Brinca A, Gonçalo M. Patch testing in fixed drug eruptions—a 20-year review. *Contact Dermatitis.* 2011;65(4):195-201. doi:10.1111/j.1600-0536.2011.01946.x
5. Özkaya E, Elinç-Aslan MS. Pseudoephedrine may cause "pigmenting" fixed drug eruption. *Dermatitis.* 2011;22(3):E7-E9. doi:10.2310/6620.2011.10119