A 25-year-old female came with complaints of a few fluid-filled lesions located over her wrist, back and fingers associated with burning and itching since one day. She stated that these lesions had appeared within a few hours of taking a single dose of oral doxycycline which was prescribed to her by an ophthalmologist for recurrent chalazion along with topical steroids for a few days. On deep probing, she recollected to have had a previous episode of a similar reaction at the same site after taking the same drug 3 years back which healed with residual pigmentation. Her medical history was insignificant. The patient denied taking any concomitant drug or any other new drug in the preceding days.

Cutaneous examination revealed a well-defined oval, erythematous, bright red patch measuring about 2–2.5 cm with central vesicle and erythematous halo over the left wrist and the left little finger and lesion with central violaceous hue and halo of pallor with peripheral erythema over the back [Figure 1]. Complete blood count and biochemical investigations were normal. A biopsy from the lesion showed a few necrotic keratinocytes with hydropic degeneration and superficial dermal infiltrate of admixture of lymphocytes with few eosinophils and neutrophils along with melanin incontinence in the upper dermis [Figure 2]. Thus, based on history and examination, a diagnosis of fixed drug eruption (FDE) to doxycycline was made. The patient was told to stop the offending agent and was started on oral antihistamine and topical steroid with complete recovery of symptoms in five days.

Doxycycline was thought to be the causative agent for FDE in this patient based on history and clinical criteria. However, the patient did not consent for a provocative test or a patch test. Naranjo algorithm for causality assessment revealed a score of 9.

**QUESTIONS**

- Why the diagnosis of FDE was made in this case?
- Which are the other causative agents implicated in causing FDE?
- If this patient requires antibiotic or pain relievers what drug substitution should be done in this case?
- What are the mechanism and different types of FDE?
- How can FDE can be prevented in future?
- Are there any reliable diagnostic tests for confirming the diagnosis and identifying causative agent of FDE?
ANSWERS

Why the diagnosis of fixed drug eruption was made in this case?
Within a few hours of intake of doxycycline, the patient developed the fluid filled lesions associated with burning and itching over the wrist, trunk, and finger. There was no history of any concomitant drug intake with this medication as well as the presence of significant temporal correlation between the intake of drug and occurrence of the classical target like skin lesions. Furthermore, there is significant history of the similar episode on intake doxycycline as per history of the patient. In addition, previous reports of similar adverse cutaneous reactions due to suspected drug in the literature helped in making causality assessment. Naranjo’s score for doxycycline was 9 indicating “definitive” causal association.

Which are the other causative agents implicated in causing fixed drug eruption?
The most common drugs causing FDE are antibiotics such as trimethoprim-sulfamethoxazole, penicillin (amoxicillin, ampicillin), fluoroquinolones, tetracycline (minocycline, doxycycline), erythromycin, followed by nonsteroidal anti-inflammatory drugs (NSAIDs; diclofenac sodium, aspirin, naproxen, and ibuprofen). Other drugs implicated include metamizole, phenylbutazone, paracetamol, mafenamic acid, metronidazole, tinidazole, chloromezanone, belladonna, griseofulvin, phenobarbitone, diflunisal, pyrantel pamoate, clindamycin, allopurinol, orphenadrine, albendazole, dapson, phenolphthalein, oral contraceptives, phenacetin, pannycin, sulfonamide, sulfasalazine, benzodiazepines and chlor Diazepoxide, hyoscine butylbromide, and quinine[2,3].

If this patient requires antibiotic or analgesics what drug substitution should be done in this case?
The offending drug should be strictly avoided. Alternative antibiotics such as cephalosporins, aminoglycosides, macrolide group can be prescribed, though FDEs to macrolides have also been occasionally reported. Hence, safer alternatives include azithromycin, clarithromycin, aztreonam, and linezolid.

NSAIDs-induced FDE seems to be selective and according to some studies, it does not show a cross-reactivity between the drugs. Alternative preparations for pain relief include tramadol, newer selective COX-2 inhibitors such as etoricoxib, rofecoxib, although a few reports of FDEs secondary to its use do exist.

What are the mechanism and different types of fixed drug eruption?
FDE is believed to be a lymphocyte CD8-mediated reaction; wherein the offending drug may induce local reactivation of memory T cell lymphocytes localized in epidermal and dermal tissues and targeted initially by the viral infection.[5] Certain individuals may be genetically predisposed.[6]

The offending drug probably acts as a hapten which preferentially binds to basal keratinocytes, eliciting an inflammatory response.[7] Through liberation of cytokines such as tumor necrosis factor-alpha, keratinocytes may locally up-regulate expression of the intercellular adhesion molecule-1 (ICAM1).[8] The up-regulated ICAM1 has been shown to help T cells (CD4 and CD8) migrate to the site of an insult.[9,10]

CD8 cells perpetuate tissue damage by producing inflammatory cytokines interferon-gamma and tumor necrosis factor-alpha. CD8 cells isolated from active lesions have also been shown to express alpha E beta 7, a ligand for E-cadherin, which may further contribute to the lymphocyte’s ability to localize to the epidermis. Other cell surface molecules, such as CLA/alpha4beta1/CD4a that bind E-selectin/vascular cellular adhesion molecule-2/ICAM1 help to further attract CD8 cells to the area.[11]

Changes in cell surface markers allow vascular endothelium to select CD4 cells for migration into active lesions. These regulatory CD4 cells likely produce interleukin 10, which has been shown to help suppress immune function, resulting in a resting lesion.[11] As the inflammatory response dissipates, interleukin 15 expression from keratinocytes is thought to help ensure the survival of CD8 cells, helping them fulfill their effector memory phenotypes. Thus, when re-exposure to the drug occurs, a more rapid response develops in the exact location of any prior lesions.[11]

FDE characteristically recurs in the same site or sites each time the drug is administered, and the number of sites may increase with subsequent exposure.[1] FDE presents mainly as sharply marginated, round or oval itchy plaques of erythema and edema becoming dusky violaceous and sometimes vesicular or bullous.[1] Most of the reactions occur within 30 min to 1 day of drug exposure.[3] The lesions may be solitary or multiple. The most common sites are the genitalia in males and the extremities in females.[3] Lesions can also be seen on the oral cavity, perianal, periorbital, and trunk.[1] They may be bullous, pigmented, or nonpigmented. Pigmented lesions can be seen in pigmented individuals and heroin addicts. Nonpigmented lesions are reported with pseudoephedrine use.[12]
How can fixed drug eruption can be prevented in future?
Once it is confirmed that patient has FDE due to a particular drug, the patient should be counseled and educated about it and explained that such episode may recur in future with intake of offending drugs. A drug allergy card should be given to patient mentioning offending drug. Patients should be instructed to show this card to doctors if they are required to take medications for any ailment. Desensitization to medications has been reported in the literature, but this should be avoided unless no substitutes exist.

Are there any reliable diagnostic tests for confirming the diagnosis and identifying causative agent of fixed drug eruption?
Certain causality assessment scales regarding drug reaction have been described like the Naranjo adverse drug reaction probability scale or the WHO-UMC causality assessment system. In our case, the association was “definite” and “certain” as per the Naranjo scale and WHO-UMC causality assessment system, respectively. For nonimmediate drug reactions such as FDE, patch tests, together with delayed reading intradermal tests, lymphocyte transformation tests, and oral challenges can be used in selective cases.

Rechallenging the patient to the suspected offending drug is the only known test to possibly discern the causative agent. Patch testing of the suspected drug to lesional and nonlesional skin has been helpful in a few instances. The exact protocol of patch testing is varied. Patch testing and oral provocation have been used to identify the suspected agent, especially when more than one offending agent is suspected as well as to check for cross-sensitivities to medications. A refractory period has been reported in FDE; therefore, a delay before and between patch testing and oral provocation is recommended. One study used an 8-week time window after lesion resolution and between tests, which yielded positive results. Patch testing must be performed on a previously involved site; otherwise, a false-negative result is likely. Some locations may be inappropriate for patch testing; thus, clinical discretion is advised. Once patch testing is complete, oral provocation should follow, with the least likely culprits and the negative patch test agents first, followed by more likely causes. Oral provocation is thought to be the only reliable way to diagnose FDE.

A biopsy to confirm the diagnosis should be done when diagnosis is doubtful, especially when presentation is atypical or in case of nonpigmented FDE. Histopathologic findings of FDE are characterized by basal cell vacuolization with pigment incontinence. Scattered necrotic keratinocytes with eosinophilic cytoplasm and pyknotic nucleus in the epidermis. Infiltration by lymphocytes, histiocytes, and neutrophil polymorphs is evident in the upper dermis.

How fixed drug is treated?
Acute episode of FDE is treated with antihistamines and topical corticosteroids when FDE is mild or when skin or mucosal involvement is limited. When lesions are multiple or extensive and when mucosal involvement is severe, even a short course of systemic corticosteroids can be used. In our experience, cyclosporine has also been useful in the treatment of FDE. There are several reports of FDE due to cetirizine, levocetirizine with cross-reactivity to other antihistamines in piperazine group like hydroxyzine. In such cases, piperidine antihistamines like fexofenadine or loratadine can be given.

Postinflammatory pigmentation due to FDE is dermal and thus very difficult to treat. It fades eventually over a long period.

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Conflicts of interest
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