Journal of Pakistan Association of Dermatologists. 2024;**34(3)**:649-656.

Original Article

Fixed drug eruptions with diverse cutaneous manifestations: Tracing the offending drug was difficult task

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Abstract

Objective Fixed drug eruption is a common dermatological skin problem with acute and chronic consequences and with different clinical manifestations. The offending drugs are numerous but it is often difficult to specify them in many cases. The purpose of the study is to collect a large series of patients to clarify the difference between new and old clinical manifestations and to pinpoint the offending drugs.

Methods This is a case series descriptive study where all patients with certain diagnoses of fixed drug eruption that were seen during the period from January 2014 to June 2023 were collected and analyzed regarding the demographic and clinical features. In addition, a full clinical examination was carried out including the acute, recurrent and chronic sequelae. The tracing for the insulting drugs was tried in the new and old cases.

Results The analysis of 68 cases revealed that their ages ranged from 10-55 years, with males to female's ratio of 2:1. The disease was acute in (88.2%) patients, and characterized by dusky red patches, or bright red. Also, some lesions were dusky red bullous. Frequently associated with itching and burning. The chronic cases showed well circumscribed patches and macules with deep dermal melanosis. The common sites of lesions were penile in 33.82%, trunk in 17.64%, lips in 14.7%, hands in 11.76%, face in 7.35% of cases. The offending drugs were only detected in 5 (7.35%) participants.

Conclusion Fixed drug eruption is a common cutaneous medical problem with diverse clinical manifestations and on healing, leaves permanent or long-lasting dermal pigmentation. Tracing for the offending drug is very difficult.

Key words
Fixed drug eruptions; Red bullous rash; Dusky red patches; Dermal pigmentation.

Manuscript
Received on: August 24, 2023
Revised on: December 30, 2023
Accepted on: April 19, 2024

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Introduction

The term fixed drug eruption (FDE), or "eruption érythémato-pigmentée fixe" was named by Brocq in 1894.[1] He described round or oval edematous plaques, which varied in size from that of a coin to that of a palm; that recurred on various parts of the body. As the eruption subsided, a pigmentation of variable shades and duration may persist.[1]

FDE is defined by the same-site recurrence of a rash every time a medication is taken. With any new intake of the culprit medication, the lesions may increase in size and number.[2] The typical shape of FDE is a single, well-defined erythematous to violaceous, round to oval patch with a dusky center.[3] After the acute inflammation has ended, post-inflammatory hyperpigmentation typically remains for weeks to months.[4] FDE may occur at any age, but mainly in ages from 35 to 60 years and both sexes are equally affected.[5,6] Many atypical variants may cause misdiagnosis like psoriasiform, cellulitis-like, papular, non-pigmenting, and bullous.[7-11]

More than 100 drugs can induce FDEs, but some of the most suspected drugs include sulfonamides, naproxen, ibuprofen, tetracyclines, other antibiotics (ampicillin, metronidazole), and barbiturates. The rash is usually misdiagnosed as insect bites, hives, or others because they are uncommon drug eruptions, with many variants.[12] They may occur at any site of the body, like the face, tongue, hands, feet, torso, extremities, and genitalia.[3] A careful history and clinical exam can yield recognition and discontinuation of the causative drug, which is the treatment for FDE. It is difficult to pinpoint the causative drug and the phenomenon of cross-sensitivity and polysensitivity may complicate the condition.[13]

Some foods can induce a rash similar to FDE called food fixed eruption (FFE) as was coined by Kelso in 1996 following ingestion of a certain diet rather than a drug.[14] Examples are lentil, asparagus, strawberry, tonic water, cashew nut, lactose and cheese crisps.[14-16]

Diagnosis relies on the history of drug intake and is confirmed by the resolution of signs and symptoms when the drug is withdrawn. Sometimes provocative and challenging tests are used. Although could be risky for patients, these are important to distinguish FDE from other disorders like bullous pemphigoid, cellulitis, drug-induced bullous disease, erythema multiforme, psoriasis, Stevens-Johnson syndrome, toxic epidermal necrolysis, eczema, herpes simplex and lichen planus.[17]

In cases of uncertainty or for very rare variants of FDE, a biopsy can be obtained, which would show in established lesions interface dermatitis, basal cell degeneration, dyskeratosis, and a superficial perivascular lymphocytic infiltrate with rare eosinophils or neutrophils. In late hyperpigmented lesions, there are dermal melanophages with minimal to no interface dermatitis seen.[18]

However, it is a recurrent problem in dermatology to see lesions of FDE where the patients deny taking any medicine and where provocative tests by mouth are negative. It is very likely in these cases that food dyes, confectionery and others may be the cause of the rash, even though the patients may be unaware of having taken them.[19]

Immunopathogenesis could not be explained but the widely accepted hypothesis consists of the emergence of a cell-mediated cytotoxic mechanism as a response to the presence of specific drugs that act as a hapten developing these cutaneous eruptions.[20] The activation of cytotoxic CD8+ memory T cells located in the epidermal basal layer in FDE lesions act as double-edged weapons that might have both a destructive and protective role in the skin immune system.[20,21] During 24h after the medication uptake, these T cells get activated. These cells increase the expression of intercellular adhesion molecule-1 (ICAM1), promoting the CD8+ cells' infiltration to the affected site.[22] This activation has as a response, the release of a series of cytokines such as tumour necrosis factor-alpha (TNF α), interferon-gamma, perforin and granzyme B and

the conversion of these cells to a natural killer cell phenotype by the expression of the molecule CD56 on their cell surface.[23,24] These cytokines, together with the CD8+ cells, kill the cells localized around FDE, leading to the epidermal necrosis typical in these lesions being responsible for the destructive role.[20,21]

After the protective T cells end the acute phase of FDE, the damaging CD8+ cells lose their natural killer phenotype acquired previously.[20,25] CD4+ cells keep producing IL-10 to suppress the immune function and generate a resting lesion while the inflammatory response caused by CD8+ cells is resolved. However, CD8+ effector memory T cells will persist quiescent in the basal layer of the epidermis at the affected area, which could start the reaction again by releasing more cytokines if the patient is re-exposed to the same drug.[23]

The objective of the present study is to describe the cutaneous manifestations of FDE, especially cases with odd presentations and also to trace the offending causative drugs and other provoking agents.

Methods

This is a case series descriptive study, where all patients presented with FDE, at a private clinic (KES) and Baghdad Teaching Hospital, Baghdad, Iraq during the period from January 2014 to June 2023. Established cases of FDE were collected and analyzed regarding the demographic and clinical features. A detailed history was taken regarding, age, sex, duration of lesions (if less than two weeks were regarded acute, while more than this were chronic), type of medications received, previous similar lesions, number of lesions, associated symptoms like itching, burning and tenderness. Patients were asked to declare any constitutional symptoms during the eruption. A full clinical examination was done including the shape, size, number, color and site of lesions. Also, there was an inquiry about the acute and chronic consequences of the lesions. Tracing for the offending drugs or foods was tried in the new and old cases. Written informed consent was obtained from the participants or their parents after giving a full clarification of the nature of the report as well as information of the publication of data and digital photographs, both the acute and old ones.

Results

A total of 68 cases were involved in this study with ages ranging from 10- 55 years with a mean of 23 years. They were 46 (67.64%) males and 22 (32.35%) females with M: F ratio of 2:1. The course of the disease was considered acute when the patient was seen within the first two weeks and this was detected in 60 (88.2%) patients, while chronic in 8 (11.76%) cases that were seen after 2 weeks (**Table 1**). The acute lesions presented dusky red patches in 38 (55.88%) cases, and some with bright red lesions in

Table 1 Shows the data and frequency of the involved sites in 68 patients with fixed drug eruption.

Data	*N (%)*
Males	46 (67.64%)
Females	22 (32.35%)
Acute < 2 weeks	60 (88.2%)
Chronic > 2 weeks	8 (11.76%)
Sites of involvement	
Penis	23 (33.82%)
Trunk	12 (17.64%)
Lips	10 (14.7%)
Hands	8 (11.76%)
Face	5 (7.35%)
Forearms	4 (5.88%)
Legs	2 (2.94%)
Scalp	2 (2.94%)
Feet	2 (2.94%)
Oral	1 (1.47%)
Clinical presentations	
Dusky red	38 (55.88%)
Bright red	17 (25%)
Black pigmentation	8 (11.76%)
Bullous	5 (7.35%)
Generalized	3 (4.41%)

Figure 1 Dusky red FDE of glans penis(A), a bright red rash of FDE on the flank (B).

Figure 2 Generalized FDE rash of the trunk.

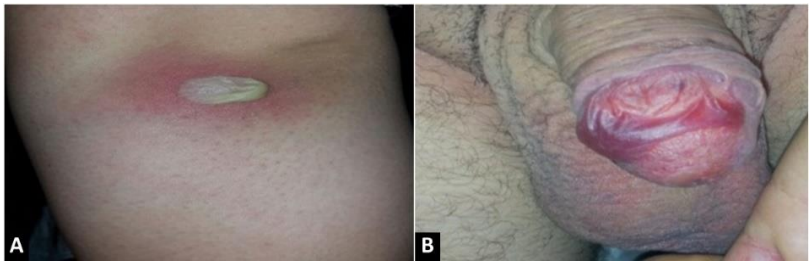

Figure 3 Bullous FDE of the leg (A), and penis (B).

Figure 4 Permanent dark black pigmentation of lips following FDE.

17(25%) with patients **(Figure 1)**. The rash was generalized in three subjects (4.41%) **(Figure 2)**.

Also, 5 (7.35%) cases were seen with dusky red bullous rash (**Figure 3)**. While the chronic cases showed well-circumscribed patches and macules with deep dermal melanosis in 8 (11.76%) cases **(Figure 4)**. The associated symptoms in almost all acute patients were itching and burning. The most common sites of lesions were the penis in 23 (33.82%) cases, followed by the trunk in 12 (17.64%), lips in 10 (14.7%), hands in 8 (11.76%), face in 5 (7.35%), forearms in 4 (5.88%), legs 2 (2.94%), scalp in 2 (2.94%), feet in 2 (2.94%) cases and oral in 1 (1.47%) (**Figures 5-8)**. Regarding the offending drugs, only a minority of patients tracing for drugs was fruitful, as patients either took multiple drugs or didn't know or forgot. Only 5 (7.35%) cases of 68 patients clarified that they used certain medicines, 3 (5%) of them gave a history of ingestion of sulfa drugs, another 1 (1.47%) used doxycycline and one used NSAID.

Discussion

Fixed drug eruption is an interesting topic for many reasons; since it is a relatively common dermatological complaint, it has variable presentations and puzzling etiological agents. This work aimed to shed light on the common and strange clinical presentations and try to trace the suspected offending medications. Although it is a very difficult task as patients may attribute the lesion to what they believe was an insect bite, or hives so the dermatologist must have a high suspicion and take a detailed history to look for the offending drugs with temporal relationship between drug intake and the appearance of the lesions and then establish a diagnosis of FDE. Furthermore, important questions to be raised include the history of previous lesions in the same area and if any new medications had been started recently. In addition, COVID-19 vaccination status should also be obtained as there have been cases of FDE after the Pfizer-BioNTech COVID-19

Figure 5 FDE of male lips (A), and female lips (B).

Figure 6 FDE rash of the scalp.

Figure 7 FDE of mouth and lips

Figure 8 FDE of the palms.

vaccination.[26] There are many provoking tests to establish the right diagnosis but they are not easy to be applied and misinterpreted and could be followed with relapse of the disease with its consequences.[27]

Regarding sex infliction, the present study included more males than females with a ratio of 2:1, The patients were mostly young with a mean age of 23 years. This is in contrast to a study by Heng KE *et al*.[27] who found in 123 patients with FDE, an equal ratio, while the median age at presentation was 38 years. The different sample sizes and geographical locations might explain such variations.

Fadhel *et al*. reported NSAIDs were the main cause of FDE in 51.2%, followed by antibiotics in 24.4% and other analgesics in 19.5% and the most common offending drug was mefenamic acid in 24.4% of cases.[6] The most common culprit drugs vary according to the geographic area. In another retrospective analysis of FDEs in France, the commonest drug was acetaminophen, followed by NSAIDs. Further literature review showed controversies regarding the commonest drugs responsible for the disease. Some studies found sulfonamides, tetracyclines, thiazides, ampicillins, NSAIDs, and barbiturates as the main cause.[2] Conversely the majority of participants in the present report had found more difficulty remembering or blaming any specific drug except in 5 (7.35%) cases from 68 patients who admitted the use of certain medicines, three patients gave a history of ingestion of sulfa drugs, another one used doxycycline and one used NSAID.

The etiologic agents causing FDE vary according to every country's local regulation of drug usage; these change when old drugs drop out of use and are replaced by new items with an unknown potential for causing FDE. Two things affect the number of cases of FDE induced by certain drugs: their intrinsic ability to cause this reaction, and the amount of that drug used nationwide, whether by prescription or over-the-counter purchase.[28]

In addition, we noticed that many patients, especially elderly people used many drugs simultaneously like oral hypoglycemics and anti-lipids and anti-ischemic or NSAIDs, making the differentiation of which drug was responsible for FDE very difficult. Also, the presence of certain antibiotics and their metabolites in certain beef or chicken

(antibiotics' thermostability) cooking may not fully eliminate the residual drugs, this might add to the difficulty in diagnosis and raise more suspicion about fixed food eruption.[29]

The morphology of FDE was quite variable in this study ranging from the usual form of acute dusky red patches (55.88%) and some with bright red lesions (25%) to the generalized rash in three cases (4.4%). While previous research, on the contrary, found most lesions were erythematous patches or plaque (40.3%) and the least shape was the dusky patch (3.2%). The blister/ erosion (32.3%) and the pigmented patch (24.2%) were higher than what had been reported in the present study (7.35%), (11.76%) respectively.[27]

The other strange findings in the present work were the unusual morphology of lesions, like large size patches (>10 cm in diameter) erosive and ulcerative lesions, or periorbital melanosis-like, or livedoid lesions on the dorsum of the foot. Some cases were found to have aphthous-like lesions associated with lip lesions. A teenage patient presented with perioral hyperpigmentation which resembled phytophotodermatitis. These clinical manifestations were not mentioned by most of the reported studies.

A retrospective study of 57 patients with FDE in Southern India, where one-third were found to have bullous and erosive lesions,[30] is in agreement with our study as most of the penile lesions (33.8%) were erosive. However, in one 18-year period Tunisian study of bullous FDEs, 55.6% of cases were reported to be generalized.[25] This is in contrast to the present work where only (4.4%) of patients, had generalized lesions. On other hand, the non-pigmenting variant of FDE was not reported in this study, which leaves no residual pigmentation. This was either because it is rare, or due to sample size.

A preceding study of 59 cases of FDE found that 20% were of the non-pigmenting subtype. While the present work showed that only 11.76% of cases showed pigmentary patches. The present study revealed that the associated symptoms in almost all acute cases were itching and burning while the most common site of lesions was the glance penis in (33.82%) of cases, followed by the trunk in (17.64%), lips in (14.7%), and less commonly the scalp in only (2.94%).

Earlier reports discovered that the upper limbs were the most common location in (65.9%) of patients, followed by the lower limbs in (31.7%), the face and the scalp in (29.3%) and the trunk in (26.8%) of cases.[6] However, one study reported a sex-dependent distribution of lesions, with 89% of women presenting with limb involvement (especially on the hands and feet), whereas 90% of men had lesions on the genitals. This is on the same line with the present study as we observed nearly similar findings, as many male patients developed penile lesions but it could be attributed due to a higher male to female ratio in the current study 2:1.[31] In addition, the oral mucous membranes were infrequently affected as only seen in 1.47% of cases in the present work, this is in contrast to a study that found 34.7% of patients had mucosal involvement but both studies showed the lesions were mainly erosive or aphthous-like.[32]

The published literature and the present work showed that FDE might have different and variable clinical presentations on different sites, hence these lesions might simulate many other diseases making diagnosis difficult. Accordingly, FDE should be considered as one mimicking skin diseases.[33]

Conclusions

Fixed drug eruption remains a major health problem as they are increasing in frequency as a result of using multiple drugs and with difficulty in tracing these provoking drugs. Also, the possibility of fixed food eruption in patients who deny taking medicines or are not sure about the responsible drugs creates more confusion about certain diagnoses. The food fixed eruption causes more difficulty and confusion in regards to diagnosis. The most common presentation of FDE is the acute dusky red patch on the penis.

Declaration of patient consent The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship None.

Conflict of interest Authors declared no conflict of interest.

Authors' contribution

KES, MHA, IKS, TAK: Concept, study design, data collection and analysis, manuscript writing, critical review, final approval of the version to be published.

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