CASE REPORT

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Paracetamol-Induced Generalized Bullous Fixed Drug Eruption Proven by Oral Provocation Test

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ABSTRACT Generalized bullous fixed drug eruption (GBFDE) is an extremely rare form of fixed drug eruption (FDE). In the present study, we report a case with GBFDE which presented with acral lesions after exposure to paracetamol. The diagnosis of GBFDE induced by paracetamol was confirmed after applying provocation test. Oral provocation test should be kept in mind in case of negative patch test for diagnosis of FDE.

Keywords: Delayed drug hypersensitivity reactions; paracetamol; generalized bullous fixed drug erruption; oral provocation test

Fixed drug eruptions (FDE) are the cell-mediated, delayed type of drug reactions.[1] FDEs are characterized by the appearance of a single or multiple sharply demarcated violaceous erythematous plaques that may blister and is often associated with pruritus.[1] The diagnostic characteristic is its recurrence at previously affected sites.[1] The lesions usually occur on the hip, lower back, proximal extremities, lips, face, and genitals.[2] The lesions usually develop from 30 minutes to eight hours time after taking the responsible drug.[3] Generalized bullous FDE (GBFDE) is an extremely rare form of FDE characterized by wide spread red or brown macules or plaques with overlying large flaccid bullae.[4] We herein report a case of a GBFDE following the use of paracetamol.

CASE REPORT

A 29 year old female presented to our allergy immunology clinic with painful blistering eruption affecting the acral sites. A week ago she had an intramuscular injection which was a mixture of thiocolchicoside and diclofenac sodium for low back pain in the emergency service. Within a few hours of injection, bullae developed over her acral sites. She began itching over the hands, feet and legs followed by burning sensation and subsequent devolopment of multiple fluid filled purplish lesions. The patient suffered from the similar symtoms twice after her inpatient treatment for low back pain in the neurology service 8 months and 18 months ago. According to the hospital records, the drugs used in both hospitalizations were paracetamol and thiocolchicoside. Cutaneous examination revealed multiple sharply-demarcated, round, erythematous plaques with central hyperpigmentation and bullae on hands, feet and legs (Figure 1, Figure 2). There were eroded areas formed by the laceration of bullae in the dorsal surface of both hands. Oral cavity and genital mucosa were not involved. Nikolsky's sign was negative. Blood tests were normal. She claimed that she had not been exposed to any other drug intake in the past week.

Based on the nature of lesions and recurrence of reactions after the use of the same drug , GBFDE was diagnosed. A short course of systemic corticosteroids (prednisone 32 mg daily for a week), and orally administered antihistamines (bilastine 20 mg daily)

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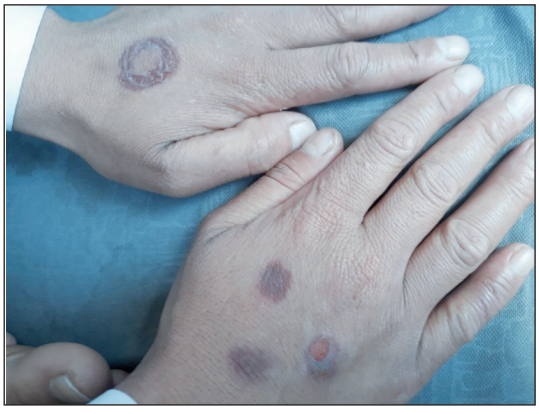

FIGURE 1: Multiple sharply-demarcated, round, erythematous plaques with central hyperpigmentation and laceration of bullae on hands.

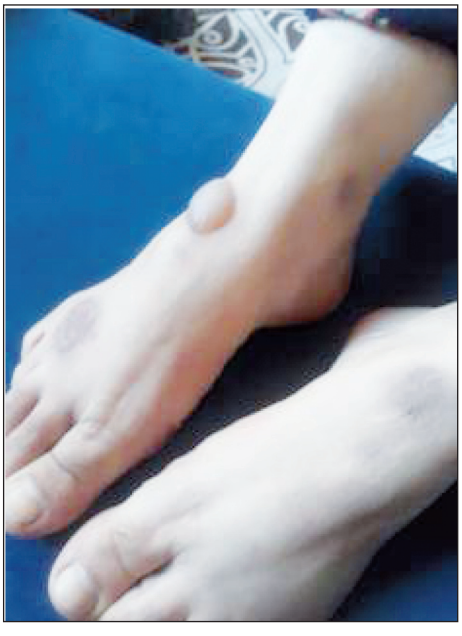

FIGURE 2: Multiple sharply-demarcated, round, erythematous plaques with central hyperpigmentation and bullae on feet and legs.

were employed as treatment modalities. Close patient follow-up revealed marked regression of lesions within a fortnight with residual hyperpigmentation.

Four weeks after regression of lesions, skin patch test was performed with paracetamol, thiocolcicoside and diclofenac. Powdered drugs were mixed with vaseline at a rate of 30% and applied to the remaining hyperpigmented areas. The results were negative.

Since the patient is a woman of childbearing age, she may need paracetamol in the future. Therefore, oral provocation test (OPT) was performed to prove that paracetamol was not responsible. One week after the patch test, OPT was started with 1/4 of 500 mg paracetamol. However, in the 40th minute of the paracetamol challenge test, severe pruritus started in the lesion areas and the test was terminated. Although no skin lesions developed, the test result was considered positive because itching developed only in the lesion areas and this was consistent with the patient's history.

Additionally, even though thiocolchicoside was thought to be the responsible drug based on the patient's history and medical records in the first place, the challenge test confirmed that paracetamol was the culprit drug.

On further inguiry, it was found out that the patient had been taking a drug including parasetamol at home just after the treatment in the emergency service.

DISCUSSION

Paracetamol is a widely used over the counter analgesic-antipyretic agent and it is known to have safety profile with very low incidence of side effects. It is also commonly used as firstline treatment of pain and fever in pregnancy.[5] Toxic eruptions induced by paracetamol are rare and usually of a fixed type.[6] GBFDE is extremely rare and, once appears, it requires differentiation from other blistering diseases, including bullous lupus ertyhematous, linear IgA bullous dermatosis and bullous pemphigoid. Differently from the other bullous diseases, FDEs may exhibit anatomical preferences to genitalia, lips, and sacrum.[7]

Patients with GBFDE can be misdiagnosed as having Toxic Epidermal Necrolysis (TEN) and Steven-Johnson Syndrome (SJS). However, in GBFDE, mucosal involvement is usually absent or mild and the clinical course is favorable with rapid resolution in 7 to 14 days after drug discontinuation.[8]

There is a characteristic recurrence at the same sites on the repeated administration of the offending drug. By contrast, recurrent lesions in SJS/TEN show nopredilection for previously affected sites. In case of a suspicion of FDE, skin biopsy can be performed. Histopathological examination was not performed in our patient.

Well general condition of the patient, history of localized lesion after drug use, absence of mucosal involvement, small body surface area, the presence of soft blisters on brownish purple patch lesions are clinical findings supporting GBFDE. Good clinical condition of our patient, history of localized lesion after drug use, absence of mucosal involvement, involvement of small body surface area, presence of soft blisters on brownish purple patch lesions are clinical findings that support GBFDE compatible with the literature.

Intraepidermal resident cluster of differentiation CD8+ T cells have been implicated in the pathogenesis of FDE.[9] When activated by certain stimuli, these cells release large amounts of inflammatory cytokines that induce inflammatory findings, such as erythema, blistering and ulceration. They also have memory and effector cell properties which are responsible for the recurrence of FDE lesions if the drug is reintroduced.[9]

Patch test positivity has been reported in 40% of fixed drug eruptions.[10] Patch test was negative in our patient. Oral rechallenge is the most reliable technique of identifying the causal agent but can be potentially injurious. To prove that paracetamol was not responsible, OPT was done but the result was positive. OPT was not started with placebo because paracetamol was not considered culprit drug. However, it is a deficiency not to start the provocation test with placebo.

Cross-reactivity is explained by the existence of similar immunogenic chemical structures within different molecules. Cross-reaction has not been reported in the literature for the development of GBFDE between paracetamol and other NSAIDs.

Priority in treatment is discontinuation of the responsible drug. In addition, mild cases are treated with topical corticosteroids while severe cases are treated with systemic corticosteroids.

Patients should be educated on the potential symptoms and signs and the chance of the recurrence of FDE after the intake of culprit medications.

Informed Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

This study is entirely author's own work and no other author contribution.

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