

CORRESPONDENCE

Generalized fixed drug eruption in a child due to trimethoprim/sulfamethoxazole

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To the Editor,

Fixed drug eruption (FDE) is a common cutaneous adverse drug reaction characterized by recurrent lesions in the same location upon repeated exposition to the causative drug. Generally, a single lesion arise but multiple lesions can also occur. Lesions heal with residual hyperpigmentation (1). More than 100 drugs are reported to cause FDE. Penicillins, tetracyclines, sulfonamides, sulfones, pyrazolones, barbiturates, and phenolphthalein are the most common culprit drugs (2). A T-cell-mediated delayed type of hypersensitivity reaction type IVc plays a role in the pathogenesis (1).

A three-year-old male patient presented with eruptions of the body, desquamation in anal region and a mouth sore. His eruptions started four days ago, 30 min–1 h after taking the first dose of trimethoprim/sulfamethoxazole which was prescribed for the treatment of acute gastroenteritis. He was seen in a public hospital where he was diagnosed with scarlet fever and amoxicillin–clavulanate treatment was started. As the patient's symptoms continued to worsen, he returned on the second day of the therapy and referred to our allergy department. Physical examination revealed rhagades around lip, an aphthous lesion on hard palate, numerous round-to-oval-shaped, reddish-brown to violaceous macules over the trunk and upper back, the biggest of which were reaching 10 × 10 cm in size, sharply demarcated reddish-brown to violaceous macules in urogenital and anal region, and desquamation in anal region (Fig. 1). Two weeks before, similar lesions appeared in the same locations after ingestion of

trimethoprim/sulfamethoxazole. His personal and family history was unremarkable.

Upon a presumptive diagnosis of FDE, the patient's antibiotic therapy (amoxicillin–clavulanate) was stopped. His complete blood count, liver, and renal function tests were normal, and viral serology was negative for CMV, EBV, herpes simplex type 1 and type 2, toxoplasmosis, rubella, hepatitis A, hepatitis B, hepatitis C, and HIV. The punch biopsy of the skin revealed keratinous plugs along the surface of the epidermis, lymphocytic infiltrate of the dermoepidermal junction and upper dermis (Fig. 2). Immunohistochemically, lymphocytes showing positive labeling with anti-CD8 and anti-CD3 were found to be abundant along the basal layer and upper dermis (Fig. 3). Lymphocytes showing positive labeling with anti-CD4 were in upper dermis.

Hydroxyzine and topical treatment with methylprednisolone aceponate were started. Anal desquamation and skin lesions started to regress within 3 days, and he was discharged but residual hyperpigmentation remained. Two months after his discharge, patch tests with trimethoprim/sulfamethoxazole, amoxicillin, and amoxicillin–clavulanate were performed according to the current guideline. Amoxicillin tablet was diluted 30% in petrolatum. Drops of trimethoprim/sulfamethoxazole (80 mg/ml), amoxicillin–clavulanate (20 mg/ml), normal saline and petrolatum (as negative controls) were applied to affected skin on the child's upper back using Finn Chambers on 12-mm adhesive tape. The occlusion time was 48 h; results were read 15 min after removing the cups and then again at 48



Figure 1 Numerous round-to-oval-shaped, reddish-brown to violaceous macules over the trunk.

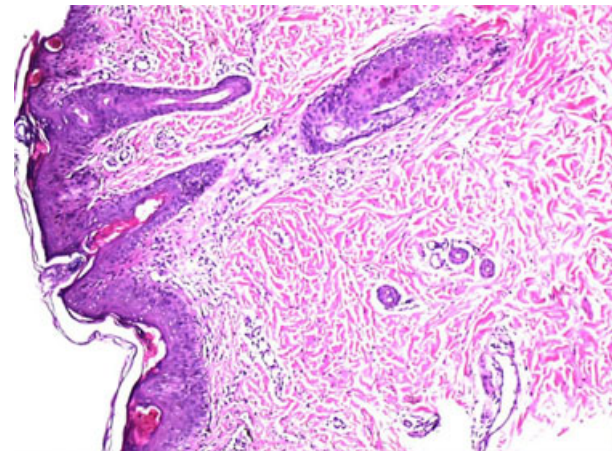


Figure 2 Lymphocytic infiltrate of the dermoepidermal junction and upper dermis (H&E 50×).

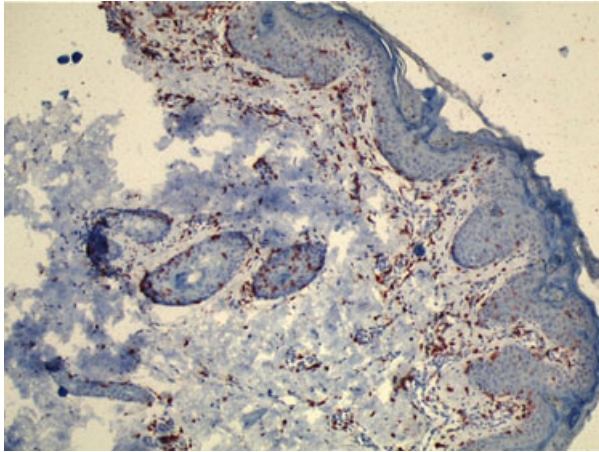


Figure 3 Immunohistochemically, lymphocytes showing positive labeling with anti-CD8 along the basal layer and upper dermis (50 $\times$).

and 72 h. No reaction was observed with amoxicillin and amoxicillin–clavulanate. Patch test showed a doubtful reaction for trimethoprim/sulfamethoxazole. An oral provocation test performed with amoxicillin–clavulanate was negative. Oral provocation test with trimethoprim/sulfamethoxazole was not performed in view of the risk of a more severe generalized reaction.

The clinical manifestation of FDE is recurrent skin lesions at the same sites after drug exposure. After intake of the drug, the lesions appear within 30 min to 8 h (1). FDE is characterized by single or multiple, round, edematous, erythematous–violaceous plaques (3). Fixed drug eruption lesions are usually single but rarely multiple lesions can occur leading to generalized FDE. Lips, hands, oral mucosa, and genitalia are the most affected sites. Lesions resolve with residual hyperpigmentation (1).

In our case, the eruptions started 30 min–1 h after ingestion of the first dose of trimethoprim/sulfamethoxazole. However, he had similar lesions at the same sites two weeks ago after ingestion of the same drug. His eruptions resolved with residual hyperpigmentation.

Histopathologic assessment of acute FDE lesions shows hydropic degeneration of basal keratinocytes associated with lymphocytic invasion of the epidermis. There are mixed inflammatory cellular infiltrates composed of lymphocytes, neutrophils, and eosinophils in the upper dermis (4). The lymphocytic infiltrate of the dermoepidermal junction and upper dermis in the skin biopsy of our patient was consistent with FDE.

The pathomechanism of FDE involves type IVc reaction (1). CD8⁺ T cells play an important role in epidermal injury. They are found in resting and acute lesions of FDE (4). When stimulated by a drug, CD8⁺ T cells produce interferon gamma, contributing to epidermal inflammation (5) and CD4⁺, CD8⁺ T cells and neutrophils are gathered in the lesions leading to tissue damage (6). Resting FDE lesions are characterized by CD8⁺ T cells aligning along the epidermal side of the

dermoepidermal junction (4). CD4⁺ FoxP3⁺ regulatory T cells are abundantly present in 24-h-old FDE lesions. The influx of CD4⁺ T cells into the epidermis can prevent injurious immune reactions mediated by intraepidermal CD8⁺ T cells (7).

In our case, lymphocytes showing positive labeling with anti-CD8 and anti-CD3 were abundant along the basal layer and upper dermis and lymphocytes showing positive labeling with anti-CD4 were in upper dermis. The biopsy specimen was obtained on day 4 after the onset. We should be aware of the fact that biopsy material represents a single time point in the development of the lesion and the phases of the FDE lesions have rarely been sufficiently defined. To identify the evolution of the lesions, sequentially biopsy specimens should be obtained (4). Nevertheless, the histopathologic findings in our patient supported the role of CD8⁺ T cells and CD4⁺ T cells in the mechanism of the disease.

The gold standard in diagnosis of FDE is systemic provocation (1). Due to the risk of severe reactions in systemic provocation, patch tests may be a safer alternative. Patch tests are recommended as the initial diagnostic tool in FDE (8). Negative systemic provocation and patch test with amoxicillin–clavulanate, doubtful reaction in patch test with trimethoprim/sulfamethoxazole suggested us that trimethoprim/sulfamethoxazole was the culprit drug in our case. We did not perform an oral provocation test with trimethoprim/sulfamethoxazole because of the risk of a generalized reaction.

Antibiotics, analgesics, antiphlogistics, and hypnotics are the most common causative drugs. Cotrimoxazole is reported among the most frequent culprit agents in FDE in Turkey (1). In our case, probably trimethoprim/sulfamethoxazole was the responsible drug.

The feature of the lesions, relationship between drug intake and the reaction onset, the remission of the lesions after drug withdrawal and healing with residual hyperpigmentation, and histopathologic findings suggested us to think that our patient was exhibiting generalized FDE.

Fixed drug eruption is a common adverse drug reaction, but generalized FDE and FDE in children are rarely seen (9, 10). FDE is a disease model for understanding the mechanism of skin inflammation elicited by skin-resident T cells (7). To understand the exact mechanism of the FDE, new studies on pathophysiology of the lesions should be carried out.

Conflict of interest

The authors declare no conflict of interest.

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