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CASE REPORT

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A Rare Case of Metronidazole Induced Generalized Fixed Drug Eruption

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ABSTRACT

Fixed drug eruption is a type of drug reaction that recurs in the same area of the body each time the offending drug is encountered. Generalized fixed drug eruption is a clinical variant of fixed drug eruption that occurs after the intake of multiple medications, characterized by multiple multifocal lesions, and is a rare condition. This case report presents a rare case of a generalized fixed drug eruption following single drug intake (metronidazole).

Keywords: Drug reactions, metronidazole, generalized fixed drug eruption

INTRODUCTION

With the increase in medication use, the frequency of drug reactions has increased, becoming a medical issue (1). Drug hypersensitivity reactions (DHRs) are responses to drugs that result in symptoms after exposure to a drug at a normal dose and are induced by immunologic pathways (2). DHRs are divided into 4 major pathophysiologic categories based on the immunologic mechanism: type I (reaction mediated by IgE antibodies), type II (cytotoxic reaction mediated by IgG or IgM antibodies), type III (reaction mediated by immune complexes), type IV (delayed reaction mediated by cellular response). Type I (immediate, IgE-mediated) DHRs such as urticaria, anaphylaxis, and bronchospasm, typically occur within 1 to 6 hours of exposure. Type IV (nonimmediate or delayed) DHRs such as contact dermatitis, fixed drug eruption, maculopapular eruption, acute generalized exanthematous pustulosis, Stevens-Johnson Syndrome (SJS) or TEN (Toxic Epidermal Necrolysis), occur more than 1 hour after exposure and frequently many days later (2,3). The most important target area of DHRs is the skin. It may be a symptom of immediate type and nonimmediate type reactions (1).

Although the rates vary in various studies, the medication most frequently causing drug eruptions include antibiotics, antiepileptics, and nonsteroidal anti-inflammatory drugs (1,4). There is no single clinical presentation for drug eruption. Although it is most commonly observed as a maculopapular drug eruption, it can also present as a severe reaction such as SJS or TEN, which can have high mortality (5).

Fixed drug eruption (FDE) is a drug reaction that characteristically recurs at the same location after re-exposure to the same medication. Lesions are usually erythematous, violet in color, sharply demarcated, and in the form of round or oval plaques (6,7). Vesicle or bullous formation may be observed at the center of the lesion. Lesions are usually itchy, and there may be a burning sensation on the lesions. The extremities, lips, oral mucosa, and the genital and perianal regions are the most commonly affected areas (8). Usually the lesions leave hyperpigmentation when the medication is discontinued. FDE can occur within hours in previously sensitized patients, and new lesions occur in the same area. Otherwise, it may take longer to manifest the clinical signs (9).

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Generalized fixed drug eruption is a rare clinical variant of FDE characterized by numerous multifocal lesions (7,10). Multiple drug exposure is a condition that generally increases drug reactions. Although it has not been determined to be a specific risk factor for type IV hypersensitivity reactions, it is observed that many patients are on multiple drugs. For example, valproic acid and lamotrigine have been shown to have a higher incidence of rash when used together than when used alone (11).

A rare case of generalized FDE occurring after the intake of a single medication is presented here. This case brings an update on the development of generalized FDE with a single drug in contrast to previous literature data.

CASE PRESENTATION

A 53-year-old female patient with known comorbidities of hypertension and carotid artery stenosis and no history of drug allergy developed generalized red lesions throughout the body and a feeling of fullness in the throat 4-5 hours after taking the second tablet of metronidazole prescribed for vaginitis. After the patient stopped taking the medication, the lesions regressed spontaneously, and she did not go to the hospital. After a 1-week break from using metronidazole, the patient restarted the metranidazole by herself due to the continuation of the vaginitis symptoms. The patient visited our clinic due to the appearance of a generalized eruption with lesions similar to the previous ones but increasing in number, itchy, and affecting many areas of the body ten minutes after taking the medication. On physical examination, purplish-colored, oval, somewhat eroded, well-demarcated plaques were observed on the dorsal surface of the hand, over the gastrocnemius, breast skin, abdominal area, volar surface of the forearm, and dorsum of the foot (Figure 1). In light of these findings, the patient was diagnosed with a generalized fixed drug eruption associated with metronidazole. Oral methylprednisolone 64 mg/day, oral antihistamine treatment levocetirizine dihydrochloride 2x5 mg/day, and topical corticosteroid treatment mometasone furoate cream (2x1 on lesions) was started. One week later, the outpatient clinic check-up revealed that the lesions had regressed (Figure 2). Oral corticosteroid treatment was discontinued on the fourteenth day according to the reduction scheme, and antihistamine treatment was continued. The lesions completely disappeared after 1 month. She was

Figure 1. Purplish-colored, oval, well-demarcated plaques on the dorsal surface of the hand, over the gastrocnemius, breast skin, abdominal area, volar surface of the forearm, and dorsum of the foot.

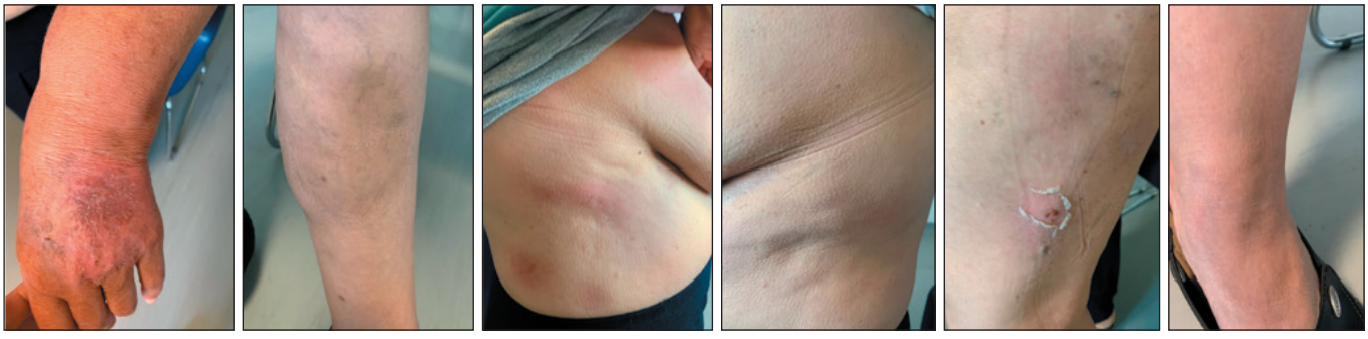

Figure 2. After 1 week of treatment, regression was observed in the active lesions as seen in Figure 1.

recommended to avoid the offending medication and provided with a written list of the generic and brand names of the culprit drug and of possibly cross-reactive drugs. She was informed about drug allergies.

DISCUSSION

With the increase in drug use, drug reactions have started to occur frequently. A good knowledge of drug reactions, and especially the early recognition of and intervention for severe reactions, is important in reducing patient morbidity and mortality.

The diagnosis is made clinically; a good anamnesis, the presence of a localized lesion in a similar area when the patient previously took the medication, and the characteristics of the lesions are important. All medications used by the patient, including herbal medicines, should be inquired in detail. Although the oral provocation test is considered the gold standard, it is not recommended due to the risk of generalized and severe reactions developing (12). In cases where the diagnosis is not clear, methods such as patch testing, biopsy, or the lymphocyte transformation test can be used for diagnosis (13).

The most important step in the treatment is discontinuing the offending medication, and reuse of the drug should be avoided. FDE can be induced by drugs with a chemical structure similar to the causative drug (cross-reactivity), and unnecessary use of medication should be avoided as lesions can be reactivated by chemically unrelated drugs (14). Topical corticosteroids are usually sufficient for mild lesions but systemic corticosteroid therapy (0.5-1 mg/kg methylprednisolone per day) may be administered in cases of severe involvement (15).

Generalized FDE is usually seen after multiple medication intake; however, in our report, it is presented as a rare case because it was observed after the intake of a single medication (metronidazole). FDE lesions usually develop 30 minutes to 8 hours after drug administration and resolve spontaneously in 7 to 10 days, leaving postinflammatory hyperpigmentation. It is noteworthy that in this case the beginning is "10 minutes". This situation can be explained by the "p-i concept" (direct pharmacological interaction of drugs with immune receptors). Clinically, the "pi-concept" can explain the sometimes rapid onset of symptoms without previous sensitization and the drug hypersensitivity immune response, with involvement of various immune mechanisms (16).

The pathogenesis of FDE is unclear although a cell-mediated cytotoxic mechanism is suggested. It is thought that the offending drug acts as a hapten that binds to basal keratinocytes. This activates cytotoxic T cells in the epidermis to release cytokines. Intraepidermal cytotoxic T cells are thought to have a key role in mediating the localized epidermal lesion that characterizes FDE (16,17).

Several variants of FDE have been reported: pigmented, generalized, linear, wandering (migrating), nonpigmenting, bullous (localized or generalized), eczematous, psoriasiform, and erythema multiforme-like FDE. It should be taken into consideration that especially cases accompanied by erosive or bullous lesions may be confused with SJS and TEN.

Generalized bullous FDE (GBFDE) is a rare and severe variant of FDE with blisters and erosions with involvement of at least 10% of the body surface area affecting three of the following six anatomic sites: head/neck, anterior and posterior trunk, upper and lower extremities, and genitalia (18). Systemic symptoms, such as fever, malaise, or arthralgias may be present. GBFDE can be misdiagnosed as SJS/TEN, but in GBFDE mucosal involvement is usually absent or mild, and the intervening areas between lesions are typically spared. The clinical course is favorable, with shorter latent periods and resolution following drug discontinuation. In SJS/TEN, lesions have a less-defined border than FDE lesions with a tendency to coalesce, mucous membranes are involved, and patients have systemic symptoms and rapid disease progression (19).

Conflict of Interest

We do not have any conflict of interest.

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Authorship Contributions

Concept: **Oyku Unsal, Filiz Sadi Aykan, Ozgur Kartal,** Design: **Oyku Unsal, Filiz Sadi Aykan, Sait Yesillik,** Data collection or processing: **Oyku Unsal, Elif Cetin Basaran,** Analysis or Interpretation: **Oyku Unsal, Sait Yesillik,** Literature search: **Oyku Unsal, Elif Cetin Başaran,** Writing: **Oyku Unsal,** Approval: **Oyku Unsal, Ozgur Kartal.**

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