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Generalized fixed drug eruption suggesting potential association with dimenhydrinate: A rare case report

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Case Report

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ABSTRACT

Generalized fixed drug eruption (GFDE) is a specific variant of fixed drug eruption (FDE) characterized by multifocal lesions that recur upon exposure to a particular medication. This report describes a rare case of GFDE in a 54-year-old male, who presented with chief complaints of widespread erythema and pruritic, burning sensation. Physical examination revealed the patient to be in generally good condition dermatological status showed erosion on the hard palate, patches, erythematous macules, and partially ruptured bullae forming erosion in inguinal and genitals area, buttocks, thighs, lower legs, feet, axillae, hands, forearms, and back. The lesions were described as purplish round/oval erythematous patches, ranging from 1-4 cm in diameter, partially confluent, forming larger areas up to 6x7 cm, with bullae partially ruptured into erosion. The patient was admitted to the hospital, and treated with Ringer's lactate infusion, and an intravenous injection of 125 mg methylprednisolone. On the second day, the dose of intravenous methylprednisolone was reduced to 62.5 mg in the morning and the patient was administered a 10 mg cetirizine tablet orally in the evening, triamcinolone acetonide for oral lesions, a 15-minute NaCl 0.9% compress on the genitals twice a day, and desoximetasone 0.25% cream for all lesions. By the third day, the patient's condition had improved, and he was then discharged. The prescribed home therapy regimen included a 16 mg methylprednisolone tablet in the morning, a 4 mg tablet in the afternoon, a 10 mg cetirizine tablet once daily, a 500 mg ciprofloxacin tablet twice daily, compress, and topical applications of triamcinolone acetonide for oral lesions and desoximetasone 0.25 % cream for all other lesions. A follow-up visit three days post-discharge indicated significant dermatological improvement. The diagnosis was established through anamnesis, physical examination, and appearance of skin disorder. Dimenhydrinate was identified as the potential causative agent.

INTRODUCTION

Fixed drug eruption was first described in 1889 by Bourns, and the term "FDE" was coined by Brocq in 1894.[1,2] Fixed drug eruption is a specific drug reaction by typical recurrence at fixed locations upon re-exposure to the causative drug.[3] Although the diagnosis of FDE is straightforward, identifying the causative agent can be challenging. Generalized FDE (GFDE) is a clinical variant of FDE, characterized by numerous multifocal lesions. The skin lesions typically appear as circular or ovoid erythematous to purplish plaques that are well-demarcated and have a generalized distribution across the skin. General FDE is rare,as evidenced by a nine-year study (2005-2014) in Iran which found only 30 cases.[1,4,5] The objective of this article is to report a rare case of GFDE with dimenhydrinate as the suspected causative drug.

CASE DESCRIPTION

A 54-year-old self-employed male presented to the emergency room (ER) of Wonosari Regional

Hospital with a chief complaint of generalized erythema accompanied by pruritus and a burning sensation for three days following the ingestion of dimenhydrinate tablets. Initially, the patient experienced burning, itchy, and crimson rashes in the inguinal region and genitals area. These rashes subsequently expanded to the feet, lower legs, thighs, hands, arms, axillae, chest, back, and mouth. In addition, the patient experienced dyspnea and dysphagia. The patient's medical history revealed that three months prior, he had similar complaints after consuming dimenhydrinate, but the symptomswere limited to the inguinal and genitals regions, so he did not seek medical attention.

Based on the physical examination, the patient was generally compos mentis with normal vital signs and good nutritional status. The general physical examination revealed normal conjunctiva, no jaundice observed in the sclera, no marked liver or spleen enlargement, and no swollen lymph glands. Dermatological examination showed lesions on hard palate, inguinal and genitals area, buttocks, thighs, lower legs, feet, axillae, hands, forearms, and back. The lesion on the hard palate was in the form of erosion; while other lesions presented as patches, erythematous macules, and partially ruptured bullae forming erosion in the inguinal and genitals area, buttocks, thighs, lower legs, feet, axillae, hands, and forearms. On the back, there were purplish round or oval erythematous patches, ranging from 1-4 cm in diameter; some partially confluent with a size of 6x7 cm, covered with bullae that had partially ruptured and developed into erosion area (Figure 1).

A preliminary diagnosis of GFDE was made based on the patient's medical history and physical examination. Complete blood count, liver function test, renal function test, and blood glucose level test result were within normal limits. The result of the posterior-anterior (PA) chest X-ray and electrocardiography (ECG) were also within the normal range. Therefore, the

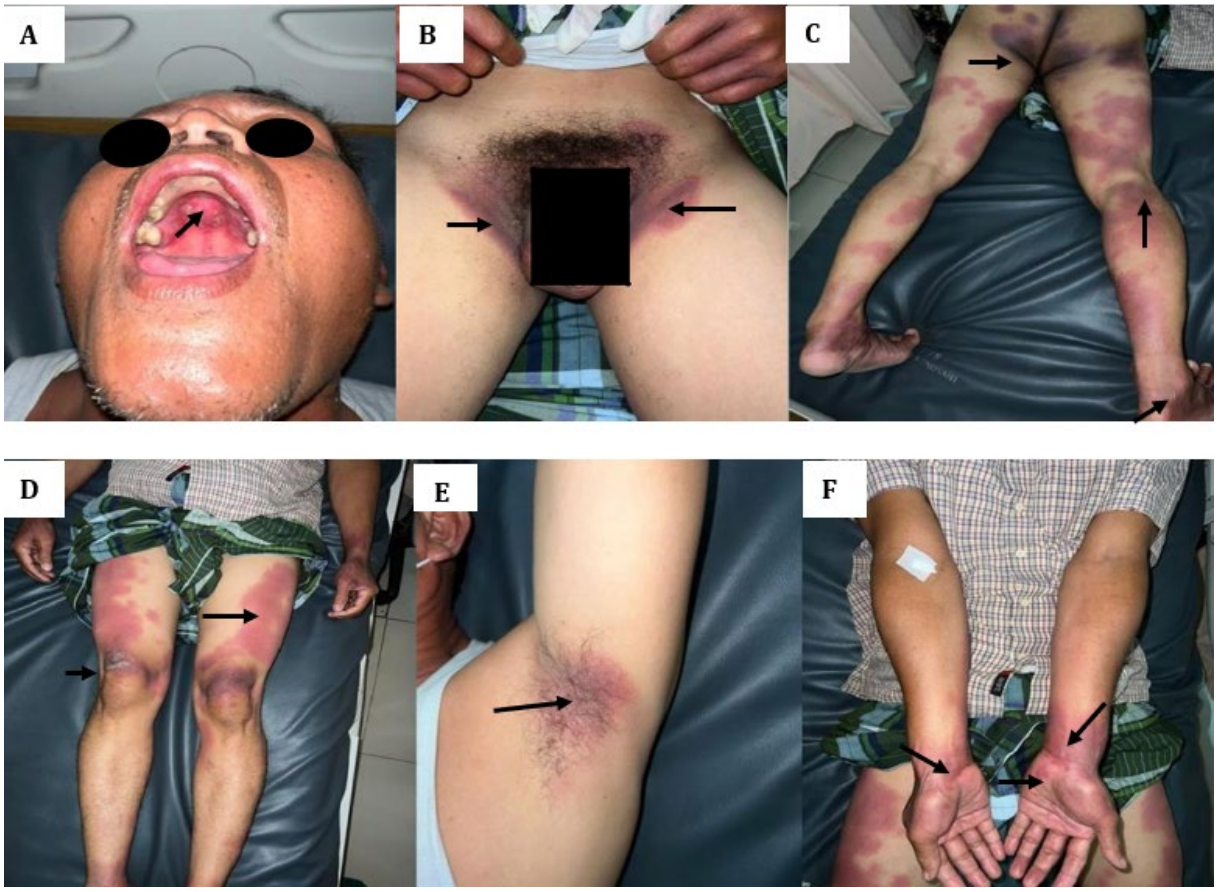

Figure 1. Patient's skin and mucous lesion (arrows): (A) Erosion on the mucosa of the hard palate surrounded by an erythematous area; (B-F) Multiple, generalized macules and purplish erythematous patches with several bullae on the genital area, lower legs, axillae, and arms.

differential diagnosis indicated GFDE, rather than Steven Johnson's syndrome, as the patient's general condition was better, the rashes were not as painful, and the mucosal lesions were not as severe. In the emergency room, the patient received initial treatment with Ringer's lactate infusion and an intravenous injection of 125 mg methylprednisolone. He was then referred to the inpatient department.

On the second day of hospitalization, the dose of methylprednisolone was reduced to 62.5 mg intravenously as no new lesions were appearing. At night, the patient received a 10 mg cetirizine tablet. Topical triamcinolone acetonide was applied for oral mucosal lesions. The patient also advised to use a physiological compress soaked in 0.9 % NaCl for 15 minutes twice daily on the moist genitals area. Desoximetasone cream was applied topically twice daily to all lesions after the 0.9% NaCl compress. This treatment continued on the third day of hospitalization. By then, the patient's condition had improved, with significant improvement in skin lesions and erosions. The patient requested outpatient treatment and was subsequently discharged.

The prescribed home-based therapy included a daily dose of 20 mg methylprednisolone, divided into 16 mg in the morning and 4 mg in the afternoon. The therapy also included a 10 mg cetirizine tablet every evening, two doses of 500 mg of ciprofloxacin, and topical triamcinolone acetonide for oral lesions. Additionally, the patient was advised to continue the physiological compress with 0.9 % NaCl on the moist genitals area, and apply desoximetasone twice daily after the compress. The home treatment was prescribed for three days, with a recommended follow-up appointment within three days post-discharge. On the third day of post-discharge follow-up, physical examination revealed improvement in the skin lessions, which had resolved, leaving only post-inflammatory hyperpigmentation (Figure 2). The patient was advised to avoid drugs that could potentially cause GFDE to prevent recurrence.

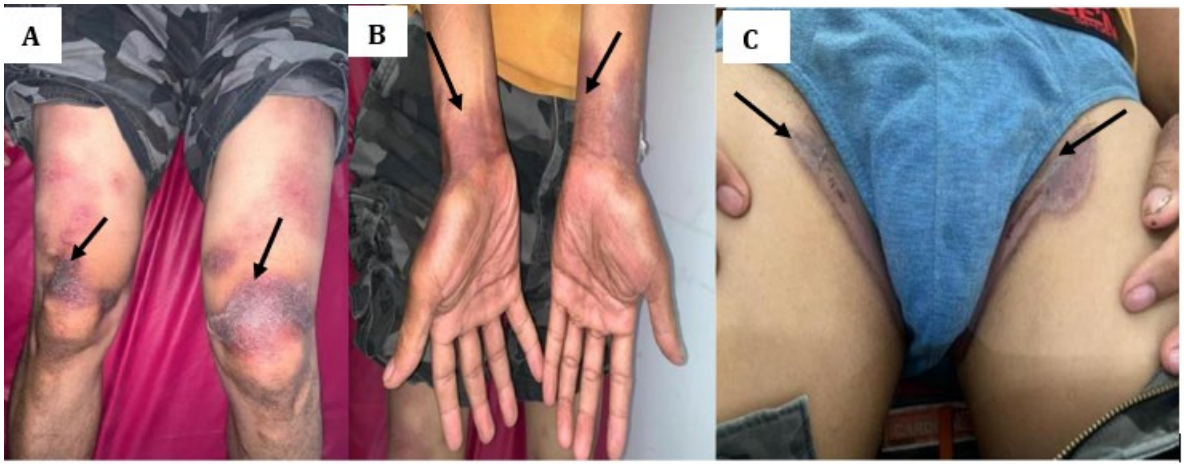

Figure 2. Physical examination on the third day post-discharge follow up showed improvement in the lesion on the upper legs, forearms, palms, and inguinal region, with multiple patches/macular erythema and hyperpigmentation with white scales on top (A-C) (arrows).

DISCUSSION

This case report presents a male patient with a rare instance of generalized fixed drug eruption(GFDE), exhibiting multifocal lesions on various location of the skin, oral mucosa, and genital area. The suspected cause is dimenhydrinate. While GFDE is not fatal, it often leads to cosmetic concerns in patients. This disorder most frequently affects individuals in their 30s, and the diagnosis can be established based on clinical manifestations. GFDE usually affects the upper extremities, genitals, and oral mucosa, typically presenting with more than five lesions. However, mucosa lesions are a more frequent in bullous fixed drug eruption than in GFDE.[1,3,6] The interval for the appearance of lesions following drug exposure is usually about two weeks, although it can occur in less than 48 hours. General FDE often results from the consumption of multiple medication or polypharmacy, making it challenging to identify the specific trigger.[2,7–11] Lesions in FDE are usually accompanied by itching and a burning sensation. The most common skin lesions are macules, patches or purplish-red

plaques with clearly demarcated boundaries that may be accompanied by vesicles and bullae, leaving hyperpigmentation after recovery.[5,8,12,13]

In this case, a 54-year-old male presented with purplish erythematous patches, some of which exhibited several bullae on top, scattered generally with multiple lesions after repeated dimenhydrinate tablet administration. Additionally, lesions were observed on oral mucosa and genital area. Lesions appeared approximately 10-12 hours after medication intake, accompanied by burning and itching sensation. The complaints and clinical manifestations were consistent with FDE lesions.

Fixed drug eruption can be classified as a type IV hypersensitivity allergic reaction to drugs.[9,12] Although the pathophysiology is not fully understood, it is believed that the process is mediated by CD8+ T cells. Upon systemic exposure to a causative agent, the agent acts as a hapten that binds to basal keratinocytes, initiating an inflammatory response. CD8+ T cells increase the production of cytokines, such as tumor necrosis factor-alpha and interferon-gamma, causing an inflammatory reaction. After cessation of the causative agent, CD8+ T cells will form memory T cells that induce a faster response upon re-exposure. Lesions usually recur in the same location as the previous reaction and appear within minutes to hours after exposure.[9,14–16]

A similar case involved a 60-years old man in Jakarta, Indonesia, who presented with patches all over his body with a dark purplish-red colour. The patient reported experiencing similar complaints after taking a non-prescribed drug consisting of thiamine, methampyrone, trimethyl xanthine, pyridoxine, and cyanocobalamin. The patient had a history of similar rashes six years earlier after consuming herbal medicine, but did not take the previous suspected drugs for current complaint. Post-inflammatory hyperpigmentation followed the previous rashes. Physical examination revealed multiple dark purplish-red macules and plaques, dense hyperpigmented macules, discoid to oval, well-poorly circumscribed across the body. Histopathological examination showed necrotic epidermis and interface dermatitis, consistent with fixed drug eruption. The patient was treated with oral prednisone 0.5 mg/kg body weight/day leading to rapid lesions improvement within three days. The patient was diagnosed with GFDE due to the pathognomonic multifocal dark purplish-red patches and extensive patterns, wuth hyperpigmented patches indicating past reaction, and a history of consuming the suspected causative drug. No exact causative substance was confirmed as the planned patch test was not conducted, though methampyrone was the strongest suspect based on previous reports.[17] Consistent with this case, the diagnosis of was based on history and physical examination, as the patient refused histopathology.

A large number and generalized distribution of lesions involving the oral and genital mucosa appeared within several hours after repeated dimenhydrinate intake. Dimenhydrinate is available as over-the-counter drugs such as Antimo®, Amocabs®, Antimab®, and Mantino®, etc. The patient consumed Antimo®, suspected to be the trigger for GFDE. General FDE is a rare variant of FDE, with a study in Iran finding only 30 cases over nine years. While polypharmacy is the most common trigger, a single drug can also trigger the disorder. Approximately 73.3% of GFDE diagnoses are based on clinical manifestations, while 27.8% rely on histopathological examination.[1,4,17–20]

Many drugs are associated with FDE, and genetic factors may play a role in its pathogenesis. Medications implicated in FDE include tetracycline/demeclocycline, feprazone, trimethoprim/sulfamethoxazole, diphenhydramine and aspirin, and ibuprofen.[2,14] Dimenhydrinate, a first-generation antihistamine, is used to prevent and treat nausea, vomiting, vertigo, and motion sickness. In some individuals, dimenhydrinate can induce allergies manifesting as rashes, though the mechanism is unclear. Fixed drug eruption after dimenhydrinate administration has been reported in only five cases (MEDLINE database from 1966 to April 2009), likely due to the diphenhydramine component in dimenhydrinate, though this remains unconfirmed. All FDE cases improve after discontinuing the causative drug and treating with topical or systemic corticosteroids.[8,19]

In this case, the patient's history indicated that red patches appeared almost all over the body, accompanied by a burning sensation after taking dimenhydrinate tablets to prevent motion sickness. Dermatological examination revealed multiple purplish erythematous patches of varying sizes, some with several bullae on the top. The lesion profile supported the description

of GFDE likely associated with dimenhydrinate. The complaints improved after discontinuing the causative drug. The patient received systemic and topical steroid therapy and antihistamine for symptomatic relief of itching. Steroid, the first-line treatment for drug eruption, were administered topically and systemically to reduce inflammation. Oral antibiotics were also administered as a precaution againts infection due to erosion lesions in multiple areas. In this case, a patch test and histopathological examination were not conducted as the patient's condition improved within three days. However, for a definitive diagnosis, histopathological examination is necessary, and a patch test is important to identify the causative substance in GFDE case.

CONCLUSION

This case report documents a male patient diagnosed with generalized fixed drug eruption, an uncommon form of fixed drug eruption, likely triggered by dimenhydrinate. The diagnosis was established through a meticulous assessment of the patient's medical history and a thorough physical examination. The patient's condition showed significant improvement with the administration of both topical and systemic corticosteroids. This case underscores the importance of comprehensive history-taking and detailed physical examination in diagnosing GFDE, especially when the gold standard of histopathological examination is not feasible. A thorough patient history is crucial to identify potential triggers of GFDE, including any previous similar symptoms or reaction. Additionally, a complete physical examination is essential to identify characteristic multiple patch lesions with a purplish-red color.

CONFLICT OF INTEREST

The authors report no conflicts of interest in this work.

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Patient has given written consent for the treatment and stated approval for scientific publication prior to the treatment.

AUTHOR CONTRIBUTIONS

The authors confirm contribution to the paper as follows: BES was involved in study conception and design, definition of intellectual content, literature search, manuscript preparation, editing and review; while TAN was involved in study conception, definition of intellectual content, literature search and manuscript preparation. All authors reviewed the results and approved the final version of the manuscript.

LIST OF ABBREVIATIONS

FDE: fixed drug eruption; GFDE: Generalized fixed drug eruption, PA: posterior-anterior; ECG: electrocardiography.

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