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Multiple Fixed Drug Eruption Due to Piroxicam: A Brief Case Report

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Abstract

Fixed Drug Eruption (FDE) is a common cutaneous adverse drug reaction. It is characterized by recurrent lesion in the same anatomical area followed by drug rechallenge. Although NSAIDs are common agents that cause drug eruptions, piroxicam is rarely reported as the causative agent of FDE in Indonesia. Piroxicam is widely used in this region for various symptoms of joint pain. We report a piroxicam-induced FDE case in this article.

Keywords: Fixed drug eruption; Piroxicam; Patch test

Introduction

Fixed Drug Eruption (FDE) is one of the Cutaneous Adverse Drug Reaction (CADR) that are often encountered by dermatologists in clinical practice. It is characterized by recurrent skin lesion at the same anatomical sites upon repeated exposures to the offending agent [1]. FDE incidence varies across the world, depending on geographical areas, socioeconomic factors, and drug prescribing patterns [2]. Analgesics and antibiotics are the most common agents in FDE. Nevertheless, only a few cases due to piroxicam has been reported so far [3,4]. We report a piroxicam-induced FDE case confirmed by topical provocation test on the skin lesions.

Case Report

A 51-year-old male presented to Dermatology and Venereology Department of Sardjito General Hospital, Yogyakarta with a history of recurrent rash since 4 years ago and usually associated with itching and burning sensation. The rash appeared several hours to one day after piroxicam intake when he felt tired or knee pain due to work. He consumed piroxicam almost every month alternate with paracetamol. When the rash appeared, he always got oral prednisolone and the complaint usually improved in 1 week. He came to hospital because of inclining number and diameter of the rash, erosion on his genital and followed by fever, nausea, and breathing difficulty.

On skin examination, well-defined hyperpigmented patches with various sizes were present over the lower lip, back, left arms, hands, including palms, genital, both thighs and legs (Figure 1). In his genital area, glans penis looks erythematous with thin desquamation and on the anterior part of scrotum, there was solitary, well-defined erosion, some with dark red crusted. We have treated patients with oral methylprednisolone 24 mg/24 hours and cetirizine 10 mg once daily for 5 days. Wet dressing with saline solution accompanied by topical momethasone furoate cream was advised for the genital lesion. Resolution was achieved after 1 week of therapy.

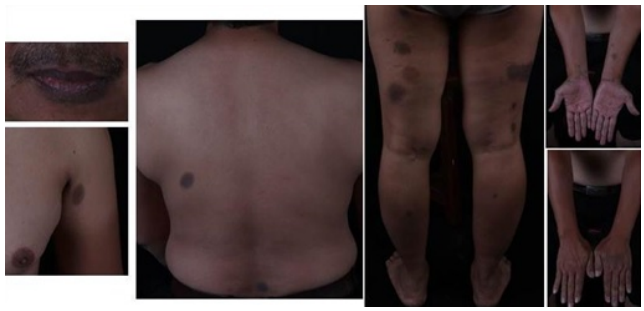

Figure 1: Hiperpigmented patches in the lower lip, right upper arm, back, and extremities.

Results

Patch test of offending drug was done 6 weeks after all the rashes have been resolved. We made a formulated drug from commercial preparation that patient usually take into two dissolutions, that are aqua and white petrolatum, each with 10% concentration. We made a dissolution in double and applied each kind of dissolution onto the lesional and normal skin. We done this application once on the first day and then we occlude with the chamber. The patch test procedure was done based on guideline [5].

Patch test readings at 48, 72 and 96 hours have shown reactivation of skin lesions applied with piroxicam 10% in white petrolatum. Reactivation was marked by well-circumscribed erythematous plaques, followed by pain and burning sensation on palpation. No similar reaction was found at non-lesional skin and at aqua based. On the skin lesions applied with piroxicam 10% in aqua, there are faint erythema and two small papules without reactivation of old lesion. Clinical relevance of this examination concluded that piroxicam is the definitive cause of FDE. Based on history taking, physical examination, and patch test result, the final diagnosis of this case is FDE due to piroxicam.

Discussion

Fixed drug eruption is a cutaneous drug reaction that is typically re-occur at the same location after repeated exposure to the causative agent. Its clinical manifestations are oval or round shaped erythematous patches and plaques with firm borders, accompanied by edema. In its development, the lesion can become vesicular or bullae. Lesions can be solitary or multiple and the number of affected areas can increase in each subsequent repeated exposure. The most common affected locations are genital areas in men, extremities in women, and lips. Lesions can also be found at the perianal, periorbital, and torso. Sometimes, lesions become exfoliated superficial erosions or ulcers with necrotic edges, especially if lesions are located in the genital area [6]. After acute phase, a typical sign of FDE is the presence of hyperpigmented residual, although in some cases there are non-pigmented lesions. FDE complaints can be varied such as heat, stinging, pruritus, or asymptomatic. Systemic symptoms are rarely found in the form of fever, nausea, diarrhoea, abdominal pain, dysuria, anorexia, and malaise [2].

The degree of sensitization in each individual determines the development of the first FDE lesion. This "incubation" period can take several weeks to several years [2]. Faster sensitization occurs in patients who use intermittent causative agents ("on and off") rather than those who use the agent continuously [1]. After the incubation period, the first lesion appears on skin and mucous membranes, 30 minutes, several hours, up to one day after exposure to the causative agent [7]. These initial lesions can appear anywhere in the body and some case reports mention that the first lesion can appear in areas of previous trauma, burns, insect bites, or vaccination [8,9]. Termination of the causative drug can cause resolution in 7 to 10 days [10].

Patient in this case had a history of recurrent lesions in the same location, and inclined at the time of recurrence at this case report. Recurrence accompanied by history of medication taken, with the average lesion appearing after one day of drug consumption. Patients also have a history of intermittent drug use, which is taking the drug when they are tired. On physical examination, lesions found in well circumscribed, oval and round hyperpigmentation patches, multiple, and spread on the torso and extremities, accompanied by skin desquamation and painful genitalia erosions. Patient also complained about fever and nausea before lesion eruption. These histories and clinical pictures are consistent to FDE manifestations with systemic symptoms.

Fixed drug eruption includes in IVc delayed-type hypersensitivity reactions. Cytotoxic T cells play a major role in this reaction [11]. The presence of T cells that reside at the site of the FDE lesion, or "pre-activated" T cells, explains why patch tests show negative results in normal non-lesion skin while the previous lesions can reactivate a few hours after attachment of the causative agent [6,12].

Systemic provocation is the gold standard for confirming the causative agent, but this test can cause a flare up reaction so the test was carried out in the form of a drug patch test with various vehicles. Positive test results were stated if an erythema reaction with a firm border remained for at least 6 hours. However, the patch test for FDE has not been standardized regarding the occlusive or open test, the concentration of the test material, and the vehicle. Considering the vehicle and location of patch test factors, it seems that the positive result is only found in white petrolatum vehicle and on the previous lesions. Reactivation of the previous lesions after provocation that is caused by T cells that reside in the area, upregulates mRNA for IFN-γ formation and releases many cytokines, and expresses FAS-ligand that binds to FAS in keratinocytes, thereby inducing apoptosis. These cells also excrete tumor necrosis factor-α (TNFα), perforin, and granzyme that are contribute to epidermal aggression. The number of CD8+ T cells are inclining for a long time after clinical resolution due to the expression of the homing receptor cutaneous lymphocyte associated antigen (CLA+) and integrin α3β7 (CD103) which bind E-cadherin to keratinocytes [6].

The site preference of FDE lesion is still unresolved, as well as the mechanism of this site preference. Previous study links different types of drugs with certain areas of the body. Tetracycline found to have significant correlations with FDE lesion on the male genitals. Metamizole was found to significantly correlate with FDE lesion on the trunk and extremities while naproxen correlate with lesion on the lips [13]. But to date no one has examined the specific location of piroxicam induced FDE lesions.

Drug concentration for patch testing in FDE cases has not been standardized. A report by the study group ENDA/EAACI in 2013 made recommendations of skin test concentrations for systemically administered drugs. They have mentioned that patch tests with up to 10% NSAIDs in petrolatum do not seem to be irritant to the skin, and drug concentration up to 30% may be tolerated [14]. From that range of values, we chose the lowest concentration of these recommendations (10% NSAIDs in white petrolatum) to reduce the possibility of irritation. We made 10% concentration of each offending drugs for testing in two different vehicle, that is white petrolatum and aqua. Although white petrolatum is considered as no sensitizing and no irritating agent, but few cases of allergic contact dermatitis to white petrolatum have been reported [15,16]. In this case, not all drugs with white petrolatum vehicle showed a positive reaction. It can be concluded that the positive reaction in our patients is not due to white petrolatum.

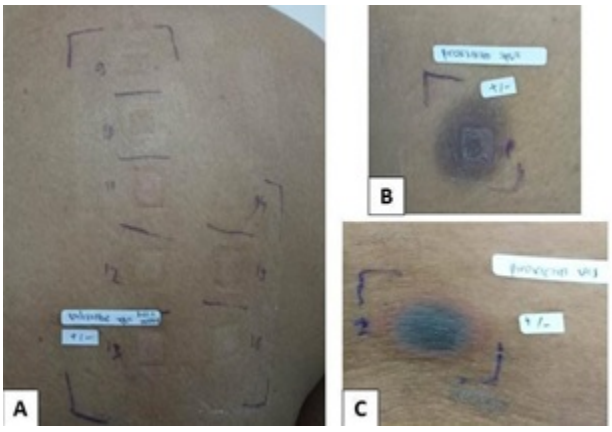

Figure 2: Patch test result in 48 hours. (A) Patch test in normal skin showed no positive results. (B) Patch test on lesional skin in upper back showed faint erythema that applied with piroxicam in aqua. (C) Patch test lower back showed reactivation of lesional skin that applied with piroxicam in white petrolatum. The patient felt pain and burn sensation in this area.

Patient in this case showed an erythematous lesion and reactivated previous lesion in the form of erythematous plaques with a firm border (Figure 2). These lesions persist until the 96-hour patch test reading

(Figure 3). This is in accordance with the reference which states that the positive results are at least 6 hours and FDE lesions generally experience resolution within seven to ten days so that the lesion will still be found on the fourth day after provocation (96 hours) [10].

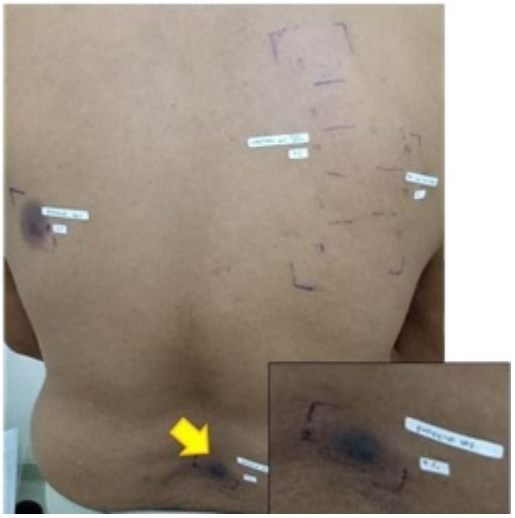

Figure 3: Reactivation of lesional skin in the lower back after 96 hours persisted.

Piroxicam is a Non-steroidal Anti-inflammatory Drug (NSAID) which belongs to the oxicam group [17]. Piroxicam has a molecular weight of 331,346 g/mol, and is currently often used as an analgesic for complaints of joint pain. Pyroxicam preparations in the form of tablets, gels, or plaster [18]. Its molecular weight of less than 500 g/mol allows piroxicam to easily penetrate the skin layer and function locally [19]. There is one report that mentions that pyroxicam-induced FDE recurrence can occur due to topical exposure in the form of piroxicam plaster [3].

Severe involvements such as multiple or generalized FDE can be treated with systemic corticosteroids for three to five days [6]. Patients in this case had a multiple FDE lesions in several body areas with systemic symptoms. Giving oral and topical corticosteroid therapy, along with antipruritus were beneficial for the patients. Resolution is characterized by the disappearance of inflammation, and can be determined through history taking and physical examination. Based on the history, the patient stated that complaints of pain and itching had disappeared. Physical examination shows that erythematous lesions have turned into hyperpigmented patches, with no change in size. This hyperpigmentation can last for years.

This case report showed one of the FDE cases due to piroxicam. The diagnosis can be made through a careful history, physical examination, and topical provocation test, namely patch test in lesional skin. Although the histopathology findings of FDE are not specific, it remains a lack of this case report that no such examination was carried out. Resolution of the lesions was achieved after 1 week of therapy.

Statement of Ethics

The authors have no ethical conflict to disclose

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors have contributions in patients' management, including doing patch test and interpretation of the patients, also revising this draft content.

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