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Case Report

Bullous fixed-drug eruption with intraoral lesions due to mefenamic acid: A case report

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Abstract Bullous Fixed drug eruption (BFDE) is a form of skin and mucocutaneous allergic reaction formed as purplish plaque or bullae with purple base in the same previous place due to certain medication. One of the drug is known to trigger FDE is non-steroidal antiinflammation drugs (NSAIDs) including mefenamic acid. Clinically, FDE is often mimic Steven-Johnson syndrome with milder clinical symptoms. A 24-year-old male came with complaint of multiple red spots with blisters and itch on his trunk, back, and leg. He also complained about his white painful scaled lip and lesion in his mouth since 1 day ago after he took mefenamic acid. The patient had the same complaint 1 year ago. Dermatological status showed multiple purpuric annular and oval well-demarcated lesions and tension bullae on his back and right leg. Less-demarcated erythema lesion were seen on his trunk. On his lips there were oedema with white desquamation and white lesions on his tongue along with multiple intraoral erosion. Blood examination showed good results. The patient was diagnosed with bullous fixed drug eruption and was treated with methylprednisolone injection 2x62,5mg with gradual tapering-off, ranitidine injection 2x50mg, and ringer lactate fluid 500cc per 12 hour. In 3 days the patient showed clinical improvement. Clinical manifestations of bullous fixed drug eruption are often mimic other dermatosis and can be differentiate with history of taking triggering medication and the place of the lesions. Education according drug-induced allergy is essential to prevent lesions recurrency..

Key words
Bullous fixed drug eruption; Drug eruption; Mefenamic acid; Methylprednisolone.

Introduction

Fixed drug eruption (FDE) was first described in the 1889 by Bourns as a sudden eruption formed as reddish rounded or oval macules or patch in the skin and mucosal membrane, leaving residual hyperpigmentation due to certain oral or injected medicines.[1] The prevalence is reported globally occurred 2-5% in hospitalized patients and 1% in outpatient. About 16-21% drug eruptions are fixed drug eruption.[2] Bullous fixed drug eruption is one of the fixed drug eruption that is rarely reported. Its clinical manifestation formed as purpuric plaque with bullae above, those make it hard to differentiate with Steven-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), and major erythema multiform.[3] According to literature, some non-steroidal antiinflammation drugs (NSAIDs) including paracetamol, naproxen, oxicam, pyrazolone derivative, and mefenamic acid have specific predilections on the lips and oral area.[4] Mefenamic acid is widely used as pain, inflammation, and fever treatment by inhibiting

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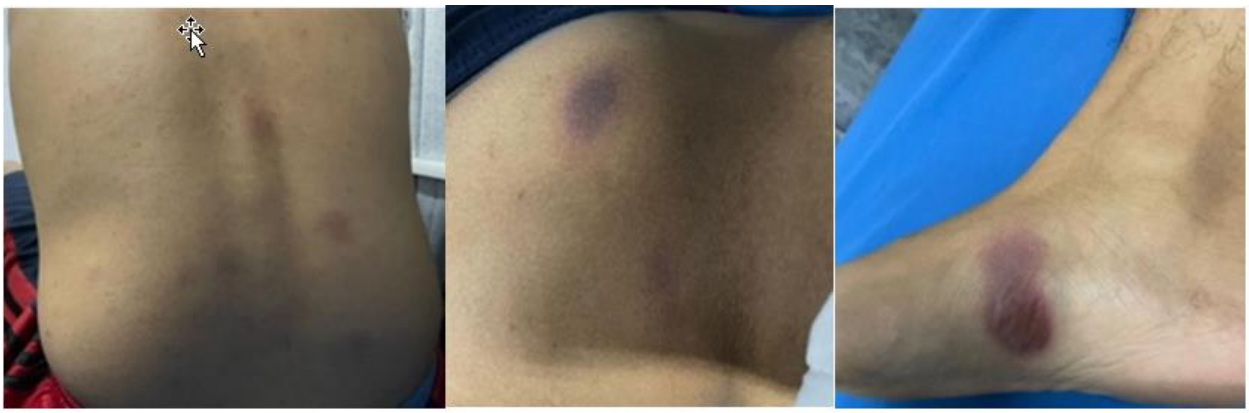

Figure 1 Annular and oval purpuric plaque on back and foot.

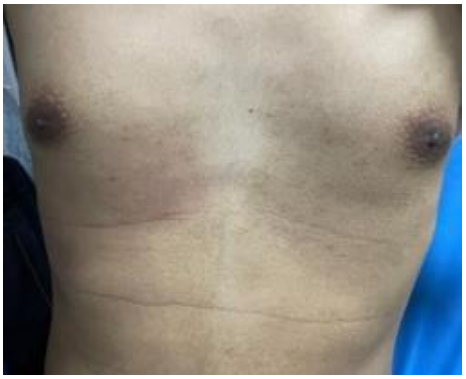

Figure 2 Localized erythema on right chest.

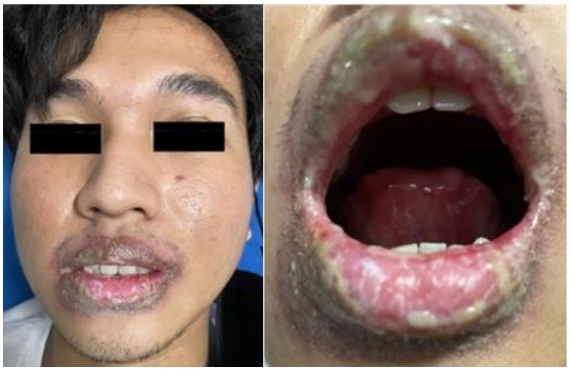

Figure 3 Lips desquamation and intraoral lesions.

prostaglandin productions.[5] As it is sold freely and sometimes is the first choice to treat mild to moderate pain, it also increases the risk of fixed drug eruptions.[6] The purpose of this case report is to described clinical manifestation of bullous drug eruption due to mefenamic acid so clinician can include this diagnosis as differential diagnosis in similar dermatoses cases, also to increase diagnostic accuracy and rational therapy selection.

Case report

A 24-year-old man came to the emergency room with complaint of itchy red spot on his back, chest, and right foot. He also complained about pain and exfoliation on his lips and white lesions in his mouth. The symptoms started one day prior his admission to the hospital after he took mefenamic acid he bought himself for his toothache. A year ago he had same complaints on his skin after he took a pain killer pill. History of food allergy, sneezing on cold weather, and same symptoms with his family are denied. Vital signs and general examinations were within normal. Dermatological examinations showed hyperpigmented centre, annular and oval purpuric plaques with sharp borders on his back and right foot in 2-3cm diameters along with tension bullae over the top. In his right chest there were localized erythema with unclear border. On his lips were seen oedema with white desquamation. Beneath his tongue were seen multiple white lesions. Other skin conditions such as squama, urticaria, erosion, excoriation, ulcer, or nodules were denied. Laboratory examinations of complete blood count, liver transaminase enzyme, kidney function, and electrolyte showed normal values. According to history taking, physical and laboratory examinations, the patients were diagnosed with bullous fixed drug eruption due

to mefenamic acid. The patients were given methylprednisolone injection 2x62,5mg with gradual tapering-off, ranitidine injection 2x50mg, ringer lactate fluid 500c/12 hours, and cetirizine tablet 1x10mg when itchy. After 3 days, the patient show significant improvement. Non-pharmacological treatment that were given to the patient was to stop taking mefenamic acid to prevent more severe allergic reaction. The patient was also suggested to do allergic test, but until this case were reported, the patient had not done the suggested test.

Discussion

Drug eruption is a form of *adverse cutaneous drug eruption*, a toxic, dangerous, unexpected reaction after normal dosage drug administration that is used as prophylaxis, diagnostic, and treatment of a disease.[7] Drug eruption are divided into 2 categories, mild and severe drug eruption. Mild drug eruptions are including urticaria with or without angioedema, exanthematous eruption, dermatitis medicamentosa, purpuric eruption, erythema nodosum, multiform erythema, lupus erythematosus, lichenoid eruption, and fixed drug eruption. Severe drug eruptions are acute generalized exanthematous pustulosis (AGEP), erythroderma, Steven-Johnson Syndrome, Toxic Epidermal Necrolysis (TEN), Lyell Syndrome, and drug reaction with eosinophilia and systemic symptoms (DRESS).[8] Some form variants of fixed drug eruptions are bullous, pigmenting, non-pigmenting, generalized multiform, multiform erythema, toxic epidermal necrolysis-like, linear, and wandering FDE.[9] Some medicines are tend to cause this reaction are antibiotic, painkiller, antiseizure, and sildenafil that are given both enteral and parenteral.[4] In FDE, the shape of drug eruptions are marked by the appearance of recurrent lesions in the same place after taking causative drugs.[1] Predilection of the lesions are on the hips, lower back, proximal extremity, and sometimes intraoral.[10] Dermatologic examination showed purpuric annular and oval plaques with clear border with tension bullae, involvement of lips mucosal and intraoral were also found, which sometimes mimic mild symptoms of SJS or TEN.[3] Nikolsky sign, Asboe-Hansen sign, and eye involvement were not found in the patient. Clinical manifestations onset of bullous FDE usually happen 30 minutes to 2 days after exposure to the causative drugs, meanwhile the onset of SJS or TEN are 4-28 days after exposure. Furthermore, there were history of lesion reoccurrence in the same site after taking mefenamic acid 1 year ago, which is a major differentiation between BFDE and SJS or TEN. The definitive examination to differentiate between BFDE and SJS or TEN is histochemical staining that will show more CD4+ cell and less CD56+ intraepidermal cell, so that granulysin epidermal cell count will be lower in BFDE than in SJS/NET.[10] In the initiating phase, CD8+ memory cells are serve as effector cell in the dermo-epidermal junction, secreting interferon-gamma due to activation of causative drugs exposure damaging epidermal layers. T-cells and neutrophil then will damage melanocyte and keratinocyte that make melanin pigment inside melanocyte disposed in the dermal layers. During resolution phase, macrophage in the dermal layers will phagocyte melanin, leading to typical post-inflammation hyperpigmentation.[7] The regenerating basal keratinocytes will secrete interleukin-15 which causes the formation of new inactive CD8+ memory effector T cells which will be activated upon repeated exposure to antigen.[10] The clinician must be able to distinguish between drug reactions and other dermatoses thus it is important to report this case. The gold standard in determining the diagnosis of BFDE is a topical provocation test (patch testing) followed by a systemic provocation test. A skin biopsy may be performed if the results of the provocation test

are unclear.[7] On histological examination of skin biopsy preparations of BFDE patients, vacuolate changes and characteristic of Civatte bodies can be found. In addition, on histopathological examination, dyskeratosis and necrosis of keratinocytes in the epidermis can be found.[3] Examination of the complete blood count for exanthema of BFDE is often inconclusive, although eosinophilia is often found.[5] The principles of therapy for BFDE are discontinuation of the use of drugs that are suspected of triggering reactions, improvement of general condition and vital signs, and administration of appropriate antiallergics. In this case the patient was treated systemically, with 2x62.5mg methylprednisolone injections, 2x50mg ranitidine injections, ringer lactate solution 500cc per 12 hours intravenously, and cetirizine 1x10mg orally if needed. After being treated for 3 days, the patient said that the itching on the body and pain in the mouth had decreased, although the hyperpigmentation of the skin was still visible. On physical examination there were no signs of secondary infection. The limitation of this case report is that topical or systemic provocation tests were not carried out after the patient recovered, so the exact cause of the drug eruption was not known. In addition, the facilities for histopathological and immunohistochemical examinations that are not available are also a limitation in ruling out the differential diagnosis. It is necessary to be aware of the possibility of cross-reaction with other NSAIDs which can cause similar lesions to appear.

Conclusion

Through this case it was concluded that the clinical manifestations of BFDE due to exposure to mefenamic acid can resemble other diseases such as SJS, TEN, and major erythema multiforme. The specific differentiator in this disease is the presence of exposure to the same drug and the location of the recurrent lesions. With the high use of mefenamic acid freely, the higher the risk of developing fixed drug eruption including the bullous form. Adequate history, physical examination, and supporting examinations are needed to avoid misdiagnosis and initiate appropriate therapy. In BFDE, it is necessary to educate about precipitating drugs so that the occurrence of similar lesions can be prevented.

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