A case report of neutrophilic fixed drug eruption

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ABSTRACT:

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Neutrophilic fixed drug eruption is a rare histopathological finding of fixed drug eruption (FDE). Whether it is a new entity or an early phase of FDE requires further investigation. We report a 34-year-old Thai female presented with multiple well-demarcated oval pruritic erythematous patches with dusky violaceous to brownish hue in the center on face, trunk and thigh. The rashes were aggravated by mefenamic acid ingestion, and improved by drug cessation. Histologic findings revealed large amount of pigmentary incontinence, also perivascular and interstitial infiltration with neutrophils and lymphohistocytes. To our knowledge, this is the first report of neutrophilic fixed drug reaction caused from mefenamic acid ingestion.

Key words: neutrophilic fixed drug eruption, fixed drug eruption, mefenamic acid

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สถาบันโรคผิวหนัง กรมการแพทย์ กระทรวงสาธารณสุข

Neutrophilic fixed drug eruption เป็นสิ่งที่พบได้ไม่บ่อยใน fixed drug eruption โดยอาจเป็นลักษณะทางจุลพยาธิวิทยาที่พบในระยะแรกของโรค fixed drug eruption หรือเป็นอีกภาวะที่แยกออกจาก fixed drug eruption ซึ่งต้องอาศัยการศึกษาเพิ่มเติม รายงานฉบับนี้เป็นการนำเสนอผู้ป่วยหญิงไทย อายุ 34 ปี มาพบแพทย์ด้วยผื่นราบรูปวงรี สีน้ำตาลเข้ม ล้อมรอบด้วยผื่นแดงราบ ที่ใบหน้า ลำตัว และต้นขา ผื่นถูกกระตุ้นด้วยการรับประทานยา mefenemic acid และดีขึ้นเมื่อหยุดยาดังกล่าว ลักษณะทางจุลพยาธิวิทยาที่พบจากรอยโรค ได้แก่ pigmentary incontinence และเซลล์ชนิดลิมโฟไซต์และนิวโทรฟิลล์รอบหลอดเลือดและแทรกตามเนื้อเยื่อเกี่ยวพันของผิวหนัง รายงานฉบับนี้รายงานการเกิด neutrophilic fixed drug eruption จากการรับประทาน mefenamic acid เป็นครั้งแรก

คำสำคัญ : ผื่นแพ้ยาชนิด neutrophilic fixed drug eruption, ผื่นแพ้ยาชนิด fixed drug eruption, ยา mefenamic acid

Introduction

Fixed drug eruption (FDE) is a common drug eruption with distinctive features. Early lesion appears as well-defined dusky-red round to oval patches or edematous plaques. Predilection sites are lips, oral mucosa, genitalia and hands. In late phase, erythematous patches turn to be hyperpigmented. Recurrence of the lesions at the same sites within several hours when re-expose to causative drugs is the most important character of FDE. Systemic manifestations are rare and varied in severity.[1] Two most common causative drug groups are antimicrobials and nonsteroidal anti-inflammatory drugs (NSAIDs).[2]

Main histopathological changes are basal cell vacuolization and pigmentary incontinence in the upper dermis. Other typical findings are dyskeratotic cells in epidermis, dermal edema, vascular dilatation with perivascular inflammatory cell infiltration predominantly consisted of lymphohistiocytes. Subepidermal bullae may develop in severe lesion.[1]

The diagnosis of FDE is based on recurrence at the same sites of pre-existing lesions after causative drug ingestion. Oral provocation test after refractory period, four weeks after resolution, is also a gold standard test for diagnosis. Specific treatment is avoidance of culprit drugs. Supportive treatment are topical and/or systemic corticosteroids.[3]

Case report

A 34-year-old Thai female presented with multiple well-demarcated oval pruritic

erythematous patches with dusky violaceous to brownish hue in the center on her forehead, trunk, right thigh and right buttock (Figure 1-4). The lesion firstly appeared at right thigh two years ago. She noticed that every time she took 500 mg tablet of mefenamic acid (Ponstan; Pfizer, Thailand) for menstrual cramp, the lesion became more red and pruritic, and new lesions also occurred within one day. Several days after drug cessation, the lesions turned hyperpigmented. She had no B symptoms. Her physical examination was unremarkable.

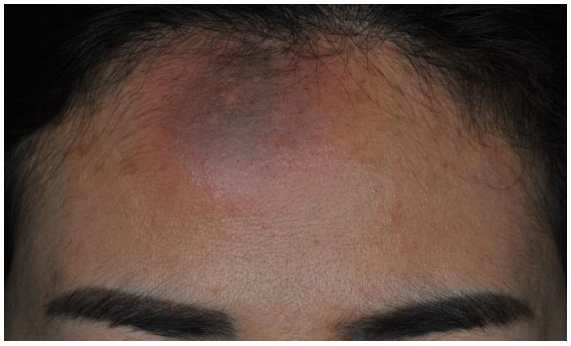

Figure 1 Well-demarcated oval erythematous patches with dusky violaceous to brownish hue in the center on forehead

Histopathological examination from the erythematous border demonstrated acanthotic epidermis with hyperkeratosis, and some degree of spongiosis with neutrophilic exocytosis. Neither vacuolar degeneration of basal cell nor necrotic keratinocyte was found. The dermis showed considerable amount of pigmentary incontinence, a superficial and mid perivascular infiltration which mainly composed of lymphocytes and neutrophils, and a few eosinophils (Figure 3-4).

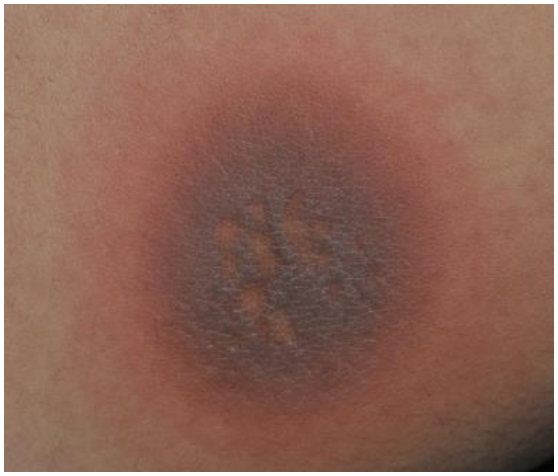

Figure 2 Well-demarcated oval erythematous patches with dusky violaceous to brownish hue in the center on right thigh, right buttock and trunk, respectively

The overall clinical manifestations together with history of recurrence at the same sites and histopathologic features were compatible with neutrophilic variant of fixed drug eruption. An oral provocation test was not feasible according to ethical consideration and patient's cosmetic concern. Therefore, the patient was advised to stop mefenamic acid ingestion. The active lesions were treated with 0.1% betamethasone valerate cream. The residual hyperpigmentation were treated with 0.05% tretinoin cream and 5% lactic acid cream. Two months after the drug cessation, neither new

lesion, nor active episode of current lesion was seen. The residual hyperpigmentation was improved thereafter.

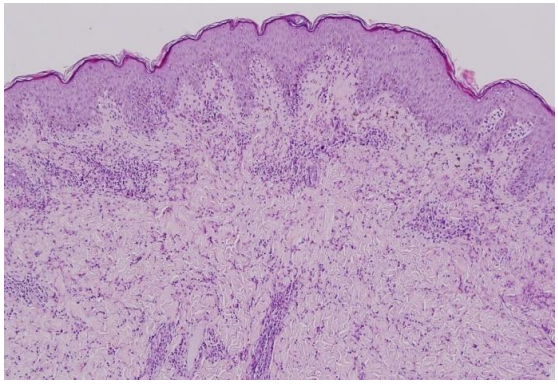

Figure 3 histopathological examination shows acanthotic epidermis with hyperkeratosis, some degree of spongiosis with neutrophilic exocytosis. The upper dermis showed pigmentary incontinence, a superficial and mid perivascular infiltration with mononuclear and polymorphonuclear cell (H&E, 10x)

Discussion

Histopathological finding from our patient's skin biopsy is not frankly compatible with classic FDE due to a large amount of neutrophil infiltration. Primarily dermal neutrophilic dermatoses without vasculitis such as Sweet syndrome, pyoderma gangrenosum, Behcet's disease, bowel-associated dermatosis–arthritis syndrome, rheumatoid neutrophilic dermatitis, neutrophilic eccrine hidradenitis are included in our differential diagnosis. The diagnosis favors FDE with neutrophil-rich histopathological finding because of reproducible typical cutaneous eruption on the pre-existing sites after the exposure to the suspected drug without other systemic involvement.

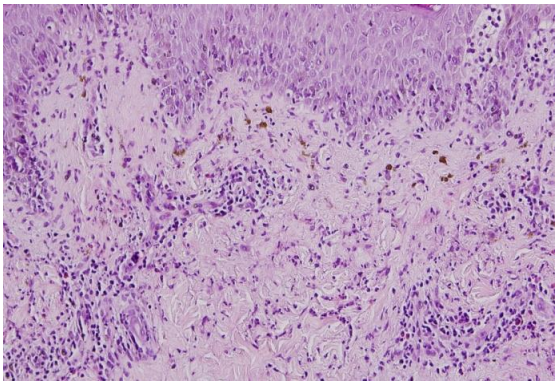

Figure 4 histopathological examination shows pigmentary incontinence in upper dermis. Perivascular infiltration with a number of lymphocytes and neutrophils. Some eosinophils are also noted within the infiltration. (H&E, 20x)

To the best of our knowledge, there were five reports on FDE with neutrophilic-rich histopathological finding (Table 1). The first report in 1984 discussed about histopathological changes in FDE at different times. The investigators found neutrophilic abscess formation in dermis at one day after the drug exposure, and classic histopathological picture of FDE appeared in the five-day-old skin lesion. They concluded that there was a dynamic cellular change in pathogenesis of FDE.[4] In 2001,

the term “neutrophilic fixed drug eruption” was coined by Agnew KL and Oliver GF. They proposed this new entity of FDE from histopathological finding in sixteen-hour-old skin lesion. The pathogenesis of this condition was thought to be antigen-stimulated neutrophilic chemotaxis without epidermal hapten formation.[5] The other reports did not mention the timing of skin biopsy.[6-8]

Table 1 Case reports of neutrophilic-rich fixed drug eruption

No.	Patients	Cutaneous manifestation	Culprit drugs	Histologic findings	Timing of biopsy	Ref.
1	79-year-old white male	- erythematous macules on dorsum of hands and leg - 3 days later, the lesions increased in number. Previous lesions developed vesicles and steel-gray coloration.	sulfamethoxazole-trimethoprim	**1-day-old lesion** - diffuse spongiosis - mononuclear cell exocytosis - dermal infiltrate of mixed inflammatory cells - dense collection of neutrophils in upper dermis **5-day-old lesion** - multiple necrotic keratinocytes in epidermis - scant perivascular infiltrate of mononuclear cells - considerable amount of melanin and melanophages	1 and 5 day	4
2	49-year-old Samoan male	indurated erythematous plaques with central flaccid bulla on lower back	amoxicillin-clavulanic acid	- collection of neutrophils and eosinophils in epidermis - basal vacuolization - perivascular infiltrate of mixed inflammatory cells - dermal interstitial infiltrate of neutrophils	16 hours	5
3	51-year-old white female	multiple indurated plaques on hands, erosion on mucosal lip	naproxen	- intense neutrophilic exocytosis and intraepidermal pustule	N/A	6
4	71-year-old white female	bright pink to red plaques without	naproxen	- neutrophilic exocytosis - diffuse dermal infiltration of	N/A	7

Table 1 Case reports of neutrophilic-rich fixed drug eruption (Cont.)

No.	Patients	Cutaneous manifestation	Culprit drugs	Histologic findings	Timing of biopsy	Ref.
		epidermal change on hip		inflammatory cells mainly composed of neutrophils		
5	27-year-old female	multiple well-circumscribed erythematous to violaceous edematous plaques with some vesicles on trunk and extremities	naproxen, metronidazole, fluconazole	- necrotic keratinocytes in epidermis - basal vacuolization with focal separation and patchy lichenoid lymphocytic infiltration - dense dermal infiltrate of neutrophils and nuclear dust	N/A	8

Our patient's skin biopsy was performed about two weeks after drug ingestion. Therefore, neutrophil-rich finding from the case supports that it was the new entity, not only early phase of FDE. However, to clarify this issue, further studies are required, for instance, sequential biopsy from the same lesion. In addition, animal model such as Yucatan micropig[9] may be used to elucidate the mechanism of this process in the future.

Mefenamic acid is an anthranilic acid derivative that inhibits prostaglandin synthesis. It is NSAID with analgesic properties which widely used for relief primary dysmenorrhea and musculoskeletal pain. In Thailand, it is one of the most common NSAID used to treat primary dysmenorrhea without medical prescription. Fixed drug eruption from mefenamic acid has been infrequently occurred.[10-16] Some variants of clinical manifestation including multifocal fixed drug eruption[11, 15, 17] and reticulated pattern[18] were also reported. To our knowledge, this is the first report of neutrophilic fixed drug reaction caused from mefenamic acid ingestion.

From previous case reports, drugs causing neutrophilic FDE include naproxen[6-8], sulfamethoxazole-trimethoprim[4], amoxicillin-clavulanic acid[5], metronidazole and fluconazole[8]. Mefenamic acid is an inducer in our patient. It appears that NSAIDs, especially naproxen are the most common culprit of neutrophilic FDE, followed by antimicrobial agents. Although it is hard to conclude with these limited data, different drugs may lead to different cell reaction, and some drugs tend to cause neutrophilic reaction in FDE.

In conclusion, neutrophil-rich histopathological picture in FDE is very rare. Whether it is a new entity or an early phase of FDE requires further investigation. The diagnosis of FDE essentially

bases on history of recurrent cutaneous eruption at the same sites after taking specific drugs rather than typical histopathological finding. Moreover, the suspected culprit drugs should be ceased as soon as possible.

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