Persistent erythema multiforme: report of a case

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ABSTRACT:

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Persistent erythema multiforme is a rare form of erythema multiforme. It usually presents with typical and atypical target lesions that occur continuously and has been related to viral infection or internal malignancy. We report a case of persistent erythema multiforme with unidentified etiology. The patient was successfully treated with prednisolone and azathioprine.

Key words: Erythema multiforme, persistent

บทคัดย่อ:

ธารทิพย์ พัฒนพงษ์ศักดิ์, นุชา เนียมประดิษฐ์ รายงานผู้ป่วย PERSISTENT ERYTHEMA MULTIFORME วารสารโรคผิวหนัง 2549; 22: 82-87.

หน่วยตจวิทยา กองอายุรกรรม โรงพยาบาลพระมงกุฎเกล้า

Persistent erythema multiforme เป็น erythema multiforme ชนิดหนึ่งซึ่งพบได้น้อย ผู้ป่วยมักมาด้วยอาการของผื่นผิวหนังที่มีลักษณะเป็น target lesion ซึ่งเกิดขึ้นอย่างต่อเนื่องตลอดเวลา และพบว่าสัมพันธ์กับการติดเชื้อไวรัสหรือมะเร็งภายในร่างกาย

ผู้เขียนได้รายงานผู้ป่วย Persistent erythema multiforme ซึ่งตรวจไม่พบสาเหตุ ผู้ป่วยตอบสนองดีต่อการรักษาด้วย prednisolone และ azathioprine

คำสำคัญ : Erythema multiforme, persistent

Introduction

Erythema multiforme (EM) is generally regarded as a self-limiting process. Acute attacks usually resolve within 3-6 weeks. In patients with persistent EM, a rare form of EM, the lesions may persist from one episode to the next. Such cases present a considerable management problem. We report a case with unknown etiology that is successfully controlled by azathioprine and prednisolone.

A case report

A 43-year-old woman presented at the Division of Dermatology Pramongkutklao Hospital with 10-year-history of necrotic skin lesions on her extremities and to a lesser extent on her trunk. The lesions spontaneously healed in about 1-6 weeks, but new lesions continued to develop. She was diagnosed as having hypertension for 8 years and her medications at presentation were hydrochlorothiazide, atenolol and amlodipine. She was otherwise healthy and had no history of recurrent herpes infection. She was treated in many clinics, the skin biopsy was done and the result was consistent with erythema multiforme (EM). Despite the treatment with oral acyclovir (800mg/day), there were no improvement.

On examination, she had multiple epidermal necrotic papules and plaques on erythematous base with some erosion, post inflammatory hyperpigmented patches and macules at upper and lower extremities, fewer lesions were on the trunk (figure1, 2). The mucous membrane were unaffected.Other physical examinations were normal. Skin biopsy from the lesion revealed basal

cell vacuolization, individual cell necrotic keratinocytes and superficial perivascular infiltration of lymphocytes and melanophages (figure 3). The clinical and histologic features were consistent with EM. So she was diagnosed as having persistent EM. The search for internal malignancy was done including pelvic examination and PAP smear, breast examination together with ears, nose and throat examinations. The results were normal.

Laboratory investigations were as followed : CBC, BUN, Cr, electrolytes, liver function test, ESR, antinuclear antibody, anti Sm, anti RNP and anti dsDNA, stool examination, chest radiography, ultrasound examination of abdomen and mammogram. All were normal. Serological tests for HBsAg, anti-HCV and anti-HBs were negative. Serology tests for HSV, CMV and EBV were consistent with past infections (HSV IgG, CMV IgG, EBV IgG were positive, HSV IgM, CMV IgM and EBV IgM were negative). Immunological studies from the lesion were all negative for IgG, IgM, IgA and C3.





Figure 1, 2 Multiple epidermal necrotic papules on erythematous base, post inflammatory hyperpigmented patches and macules at upper and lower extremities

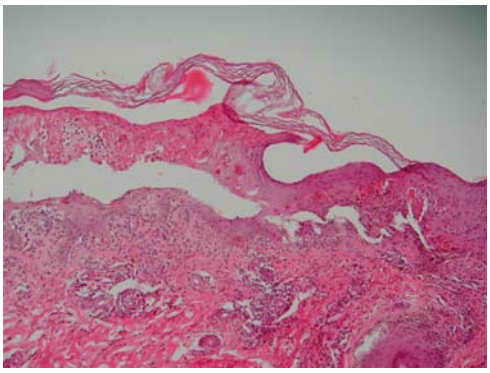


Figure 3 Skin histopathology showed basal cell vacuolization, individual cell necrotic keratinocytes and superficial perivascular infiltration of lymphocytes and melanophages.

She was treated with prednisolone 20 mg/day and acyclovir 400 mg. twice daily. The skin lesions were partially improved. Her skin eruption increased each time the dose of prednisolone was reduced, therefore we decided to treat her with azathioprine 100 mg/day and the acyclovir was discontinued. This resulted in a resolution of her cutaneous eruption and the prednisolone could be gradually tapered off.

Discussion:

The clinical spectrum of erythema multiforme (EM) can be subdivided into classical, recurrent and persistent forms. Main differential features of EM are presented in table 1[1].

Table 1 Main differential features of EM

	Classic	**Recurrent**	**Persistent**
Attacks	Sporadic	Multiple	Uninterrupted
Skin features	Papules, target lesions	Papules, target lesions	Papules, necrotic lesions
Bullae	possible	Possible	Frequent
Distribution	Symmetric, acral, mucosal	Symmetric, acral, mucosal	widespread
Photoaccentuation	Sporadic	Frequent	Absent
Koebner's phenomenon	Absent	Frequent	Absent
Duration	1-3 weeks	2 weeks	persistent
Symptoms	Absent or mild	Absent or mild	Severe
Necrotic keratinocytes	Focal	Prominent	Occasional?
Neutrophils and keratinocytes	Unusual	Unusual	Common
Hypocomplementemia	Very rare	Very rare	Common
Circulating immune complex	Very rare	Very rare	Common
Etiology	HSV, mycoplasma possible	HSV very frequent	EBV, other viruses? Other conditions

Table 2 Reported cases of persistent EM

References	Year	Patients	Precipitating factor	Treatment	Clinical outcome
Chapman et al.[7]	1997	1	Chronic inflammatory bowel disease	Gastrointestinal therapy	Couse of skin disease paralled the activity of intestinl disease
Davidson and Jegasothy[8]	1980	1	Renal carcinoma	Resection of tumor	Resolve
Russell-Jones[2]	1981	2	Non identified	azathioprine	Resolve
Leigh et al.[3]	1985	3	Non identified	Human gamma globulin	Resolve
Durha and Paul[10]	1988	1	HSV	Dapsone	Resolve
Drago et al.[9]	1992	1	EBV	Acyclovir	Resolve
Drago et al.[1]	1955	2	EBV	acyclovir	Resolve
			Gastric carcinoma	resection of tumor	Resolve
Berard et al.[11]	1997	1	Chronic hepatitis C virus infection	Interferon alpha	Resolve but relapsed after discontinued drug
Mahendran et al.[4]	2000	1	Non identified	Dapsone	Resolve
Pevlovic et al.[5]	2001	3	Non identified	methyl prednisolone	Resolve
			Non identified	dapsone	Resolve
			Influenza B virus	methyl prednisolone	Resolve
Conejo-MirJS et al.[6]	2003	2	Non identified	thalidomide	Resolve

Classical EM is an acute, self-limiting, inflammatory disorder of the skin and mucous membranes. Sporadic attacks usually resolve within 1-6 weeks but recurrences are not uncommon.

In recurrent EM, each attack lasts approximately 14 days and multiple relapses occur every year. Between each episode, however, the patient is clear of the morphologically typical lesions. HSV infection is now accepted as the commonest precipitating factor for recurrent episodes and recent studies have detected HSV in the blood during relapses using the polymerase chain reaction.

Persistent EM is characterized by the uninterrupted occurrence of both typical and atypical lesions which are widespread and often papulonecrotic or bullous that occur during several

months. It often associated with a high incidence of circulating immune complexes and hypocomplementemia. This is a very rare condition and only a small number of cases were reported in the literature (table 2)

In previously reported cases of persistent EM, investigations for the etiology are not always specified. Over half of the cases had unknown etiology[2,3,4,5,6], the rest of them had been found to be associated with chronic inflammatory bowel disease[7], internal malignancy[1,8], EBV[1,9], HSV[10] and HCV[11] infections. Chronic infection may induce immune aberration through persistent antigenic stimulation. Chapman et al[7] described a woman with persistent EM in association with chronic inflammatory bowel disease, the course of her skin disease paralleled the activity of her intestinal disease. In cases that persistent EM was associated with malignancy, the eruption resolved within a few weeks after the tumor was excised [1,8]

It appears that there are at least three subsets of patient with persistent EM (1) virus-induced persistent EM, which may or may not respond to antiviral drugs; (2) patients with some underlying disease, malignant or inflammatory, whose persistent EM generally subsides with the control of the underlying illness; and (3) 'idiopathic', probably itself heterogenous, persistent EM that is likely to respond to immunosuppressive therapy [2,5] or dapsone[4,5].

In our patient, no underlying cause for her EM has been found despite extensive investigations. She had no serological evidence of active viral infection. The lesions were widespread and resistant to acyclovir. Immunosuppression using prednisolone in combination with azathioprine was effective in this case.

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