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Case Report

Erythema multiforme: New causes and unusual presentations

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Abstract Erythema multiforme is a common reactive skin disease to different endogenous and exogenous triggers with characteristic clinical features of variable severity. The aim of the study is to draw special attention to new modes of clinical presentations and to identify new possible causes in order to increase the awareness of dermatologists.

Key words
Erythema; Multiforme; New causes.

Introduction

Erythema multiforme (EM) is an immunologically mediated, acute, self-limited, potentially recurrent skin disease that has been triggered by many infections, particularly HSV, and rarely drugs or other factors like physical trauma or environmental factors.[1-4] Two clinical types are recognized namely minor and major. Both are characterized by the same type of maculopapular lesions with characteristic targetoid or iris like center, but are distinguished by the presence or absence of mucosal involvement and systemic symptoms, which are more remarkable and severe in the major type. The diagnosis is usually made by the correlation between clinical and histopathological features. Erythema multiforme is distinguished clinically from Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) by the type of characteristic skin lesions and their distribution.[2,3,5] All EM lesions usually evolved within 24 reaching the full-blown picture at 72 hours to be resolved without any sequelae after two weeks.[6,7] The exact pathogenesis of EM is not fully understood, although it is thought to be a delayed type hypersensitivity reaction to the precipitating triggers such as the persistence HSV DNA particles in the skin that leads to recruitment of virus-specific helper 1 cells which secrets IFN gamma that results in the appearance of skin lesions.[8] Among the precipitating factors, Few cases of localized and generalized EM had been reported in association with orf , but to the best of our knowledge, no case of EM precipitated by head lice infestation was reported previously. Here in, we presented three cases of erythema multiforme; one of them is orf associated localized maculopapular erythema multiforme, while in the other two the erythema multiforme was vesiculobullous (bullous pemphigoid like). One of them was orf associated while the other was occurred in association with prolonged heavy head lice. The rationale behind reporting these cases are, the orf associated EM are not fully described and it is not well known weither the lesions are localized or generalized, in addition the generalized bullous pemphigoid like lesions were not prescribed previously. Moreover, head lice associated EM and to the best of our

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knowledge was not reported neither in literature nor in any other previous studies.

Case 1

A 55-year-old female patient, presented to outpatient clinic with a history of asymptomatic nodular lesion on the dorsum of right index finger for 14 days duration, then she started to develop itchy maculopapular skin rash for 2 days duration. The patient gave history of contact with sheep head 2 weeks ago, with negative family history of the same condition, no chronic disease with no chronic drug use. On examination, the looked apparently healthy with normal all vital signs, the skin examination revealed that there is a nodule at the dorsal aspect of right index finger with generalized bilateral symmetrical mainly acral maculopapular skin rash with targetoid character. There was right axillary lymphadenopathy with no mucous membrane involvement. All the relevant investigations and serology tests were normal. Biopsy of skin lesions, revealed that there is necrosis of the upper epidermis, spongiosis, apoptotic keratinocytes, focal vacuolar degeneration, upper dermal edema with mild perivascular lymphocytic infiltrates, which is in correlation of clinical picture, was consistent with the diagnosis of erythema multiforme. The diagnosis of orf with reactional EM was done and confirmed by positive PCR test from orf lesion. The patient was started on topical moderate potency steroid plus systemic antihistamine for 10 days duration, and then the patient returned back where all EM lesions were resolved with mild postinflammatery hyperpigmentation.

Case 2

A 23- year- old female patient presented to outpatient clinic with vesiculobullous skin lesion for 1-month duration with negative family history of the same condition, no chronic diseases and no chronic drug use. On examination, the patient looked pale with normal vital signs, there was bilateral symmetrical severe vesiculobullous lesions at acral part of extremities with involvement of palm, planter aspects of the fingers and the soles that interfere with the patient walk, some of the lesions showed central crust and umbilicated maculopapular lesions on the forearm and legs. Mucus membrane, face and trunk were normal. On examination of the scalp, there was heavy infestation with head lice with excoriation, oozing and cervical lymphadenopathy as seen in **Figure 1-3**.

Figure 1-3 (Author photo) vesiculobullous EM with heavy head lice infestation.

All related investigations and serology were normal. Skin biopsy of the vesiculobullous lesion revealed that there is necrosis of the upper epidermis, spongiosis, apoptotic keratinocytes, focal vacuolar degeneration, upper dermal edema with mild perivascular lymphocytic infiltrates, which is in correlation of clinical picture, was consistent with the diagnosis of erythema multiforme. The patient was treated with systemic ivermectin (12mg) once weekly for two consecutive weeks, systemic antihistamine, and topical drying agent in addition to antilice shampoo (twice application, one week apart) for 14 days duration where all the lesions of EM were resolved completely once the head lice was cured.

Case 3

A 37-year–old female patient presented to outpatient clinic with two nodular skin lesions for 12 days duration, and then she started to develop vesiculobullous lesions all over the body, which were itchy for 5 days duration, with negative family history of the same condition, no chronic diseases and no chronic drug use. History of contact with sheep head was positive. On examination, the patient looked normal and healthy; there was two centrally crusted nodules, one on the planter aspect of left hand, the other on the planter aspect of the right thumb and there were generalized vesiculobullous (bullous pemphigoid like) skin lesions involving mainly the extremities face and trunk for 5 days duration as seen in **Figure 4-6**, mucous membrane, scalp, and face are spared. All vital signs were normal, the relevant investigations and serological tests were normal. Skin biopsy of the vesiculobullous lesion showed that there is spongiosis, apoptotic keratinocytes, subepidermal cleft formation, focal vacuolar degeneration, upper dermal edema with mild perivascular lymphocytic infiltrates, which is in correlation with clinical picture, was consistent with the diagnosis of erythema multiforme. PCR test for orf lesions was positive. The patient treated with systemic antihistamine with topical steroid of mid potency and the patient was reassured about the orf lesions that it is a self-limiting disease to be seen 2 weeks later where all the lesions were healed completely.

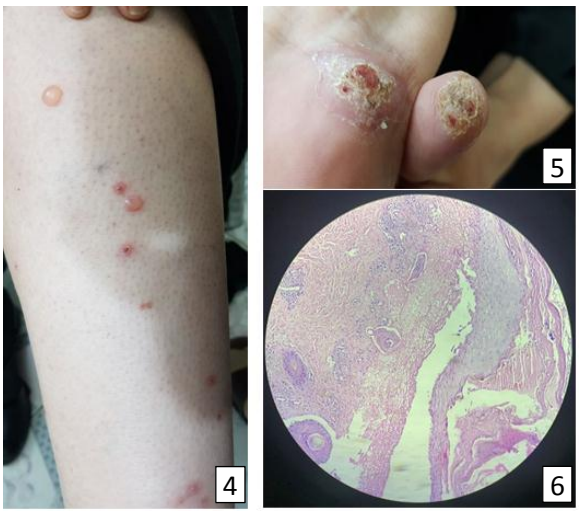

Figure 4-6 (Author photo) bilateral orf with bullous pemphigoid like EM and histopathology that revealed bullous EM.

Discussion

In the present first and third cases, Orf was diagnosed by its characteristic clinical features, positive history of contact with head of a sheep and by PCR. EM is an immunologically mediated reaction mostly due to infections especially herpes simplex and orf viruses, drugs suspected to cause EM in 10% of the cases.[9] It had been suggested that 7-18% of patients with orf would developed EM.[10] Orf associated EM is usually manifested within 2-4 weeks after the onset of orf lesions which is typically bilateral symmetrical itchy maculopapular rash with characteristic targetoid lesions that is either localized to the hands and forearm[11] or affecting areas remote from the orf lesions like legs, feet, neck and face.[11] There are six cases of widespread vesiculobullous EM eruption[12] and six cases of bullous pemphigoid after orf infection[13] in whom the patients differ from orf associated EM by severe disease and in some

cases by the requirement of immunosuppressive treatments.[13] In daily clinical practice three patterns of EM are observed where the patient present with few maculopapular and targetoid lesions surrounding the orf or the EM lesions are maculopapular of acral distribution involving mainly hands, feet, forearms, legs, and to a lesser extent the face or EM may present with typical EM lesions with a vesiculobullous pemphigoid like lesions that are generalized involving the extremities, face and trunk with or without involvement to the mucous membranes. In this series, we presented three cases in one of them the EM was maculopapular and targetoid lesions of acral distribution sparing the trunk, legs and face which constitute the typical presentation of EM that high lightened orf as a possible triggering factor of EM and one should aware of this possibility. In the other two, the lesions of EM were vesiculobullous involving in the first one acral parts only without mucous membrane, face and trunk involvement and it was precipitated by prolonged heavy head lice infestation, which is to the best of our knowledge, is the first case reported worldwide, the resolution of EM lesions by the treatment of head lice confirmed the causal relationship between EM and head lice infestation particularly no topical treatment for EM lesions was used apart from drying agent which means that resolution of EM, as a reactional disease, is mainly attributed to treatment of head lice infestation as a trigger cause. Moreover, in the third reported case, the EM lesions were generalized vesiculobullous pemphigoid like lesions involving, in addition to the acral parts, the trunk that is usually spared. The histopathological features were consistent with that of EM rather than bullous pemphigoid where it lacks the presence of eosinophils with epidermal changes that are usually normal in bullous pemphigoid lesions. Although direct immunofluresent testing was not done for our patient because unfortunately it is not available in our locality, but the rapid resolution of vesiculobullous lesions by drying agent and topical steroid without systemic steroid or immunosuppressive therapy gave a supporting evidence that the lesions were EM and not bullous pemphigoid. We thought that this case is possibly an odd presentation of EM especially only six cases of generalized vesiculobullous EM sparing the trunk were reported previously.[12] The mechanism of orf virus induction of EM is not fully understood, it had been suggested that the virus might produce immunmodulatory virulence factors that possibly interfere with host inflammatory and immune response.[14] EM induced bullous pemphigoid can result from alteration of basement membrane proteins by the virus and its similarity between the virus and these proteins.[15] For head lice as a possible cause of EM, by reviewing literature, we found that nothing is mentioned about this issue, but we thought that head lice particularly when it is severe, prolonged and complicated by secondary infection, may induce a delayed type hypersensitivity reaction to the lice, its saliva, its products and other bacterial infections associated with it, that may be manifested in many clinical features one of them is EM which is one manifestation of delayed type hypersensitivity reaction.[16]

Conclusion

EM can be triggered by un reported causes like prolonged heavy head lice infestation and manifested clinically in variable modes of presentations ranging from localized typical EM to generalized wide spread vesiculobullous pemphigoid like lesions and accordingly one should consider these possibilities in clinical practice treating the precipitating cause and the reactional lesions.

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