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HERPETIFORM ERUPTION WITH LEUKOCYTOCLASIS: A DISTINCTIVE CLINICO-PATHOLOGICAL VARIETY OF ERYTHEMA MULTIFORME

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Abstract. Six patients are described who experienced a prodromal period suggesting an infective process, followed by a distinctive polymorphous cutaneous eruption. The most striking lesion, present in all of them and giving the eruption a distinctive herpetiform appearance, included closely grouped vesicles resting on an erythematous base. Histopathological examination of these lesions showed features of dermal and epidermal types of erythema multiforme but with prominent leukocytoclasis. We suggest that the clinico-pathological picture of our patients may be considered a distinctive clinico-pathological variety of erythema multiforme.

Key words: Herpetiform eruption; Leukocytoclasis; Erythema multiforme

The cutaneous lesions of Erythema Multiforme (EM) have a varied appearance. Although its classic presentation includes concentrically ringed and target lesions, macules, papules, vesicles and bullae are all known to occur. Histologically, both epidermis and dermis may be primarily affected (1, 2, 11, 13). The more characteristic changes include: slight intracellular and intercellular epidermal edema, focal or generalized keratinocytic necrosis, extensive vacuolar alteration along the dermo-epidermal interface, edema of the papillary dermis and a lymphohistiocytic infiltrate around blood vessels and in the dermo-epidermal junction.

In this paper we describe 6 patients with a distinctive cutaneous eruption showing histological features of the dermal and epidermal types of EM (11) besides a prominent leukocytoclastic dermal infiltrate.

PATIENTS

The clinical and abnormal laboratory data are summarized in Tables I and II. All our patients were seen during the spring and summer seasons and all of them but one were female in the fifth decade (Table I). All patients but one had a prodromal period 2–6 days prior to the appearance of the characteristic eruption, consisting of fever, chills, and malaise suggesting an infective process, though no evidence of infection could be found during either the prodromal or active periods of the illness. On the other hand the occurrence of any factor known to precipitate an attack of EM could be determined. None of the patients had a history of previous drug intake. After this prodromal period all of them developed a polymorphous cutaneous eruption (Fig. 1) in which three different morphological lesions could be observed (Table II): (1) Herpetiform lesions, consisting of closely grouped vesicles on an erythematous base giving a herpetiform appearance. The vesicles enlarged gradually resulting in a multilocular blister (Fig. 2). These lesions were the only ones present in all of the patients and were always located along the extensor aspects of the arms, forearms and legs, giving this eruption a distinctive appearance.

(2) Raised erythematous plaques 2–4 cm in diameter, some of them showing a pseudovesicular border. These lesions were very similar to the cutaneous lesions of Sweet's syndrome. They were not present in all patients. When present they were observed on the sides of the neck, the lateral aspects of the face and on the V area of the upper chest (Fig. 3B).

Table I. *Data and characteristics of the prodromal period in the 6 patients*

Pats.	Sex and age at onset (yr)	Month at onset	Prodromal period (symptoms)	Duration of prodromal period (days)
1	♀ 40	July	Fever, chills, malaise	2
2	♀ 45	July	Fever, malaise, headache	4
3	♀ 48	March	Fever, chills, headache and malaise	3
4	♀ 48	March	Fever, chills, malaise	4
5	♂ 40	March	–	–
6	♀ 41	August	Fever, chills, malaise	6

Table II. *Features of the cutaneous lesions and abnormal laboratory data*

Pats.	Cutaneous lesions: Type	Cutaneous lesions: Location	Duration (days)	Laboratory ESR (mm/h)
1	Herpetiform Raised plaques	Arms, forearms and legs, V area upper chest	23	78
2	Herpetiform	Arms, forearms and legs	25	72
3	Herpetiform Urticarial plaques	Arms, forearms and legs, dorsum of hands and fingers	13 (with prednisone)	62
4	Herpetiform Raised plaques Urticarial plaques	Arms, forearms and legs, V area of upper chest, dorsum of hands and fingers, and palms	29	98
5	Herpetiform Raised plaques	Arms, forearms, legs and sides of neck, face	14 (with prednisone)	51
6	Herpetiform Urticarial plaques	Arms, forearms and legs, dorsum of fingers and palms	27	72

(3) Urticarial plaques 1 cm in diameter (Fig. 3 A). They were observed in only 3 patients and were always located on the dorsum of the hands and fingers and on the palms.

An intermittent fever accompanied the cutaneous eruption during the active phase of the illness. The highest temperature recorded was 39.8°C. The active phase of the illness (i.e. from the onset of the cutaneous eruption to the disappearance of the skin signs and fever) lasted 23–30 days, leaving a slight pigmentation, in the 4 patients to whom treatment was not given. In the 2 patients receiving prednisone, 30 mg daily, the cutaneous eruption and fever disappeared in 2 weeks.

No mucous membranes lesions were observed in any of the patients. Apart from the fever and rash, the general physical examination and chest X-ray revealed no abnormalities.

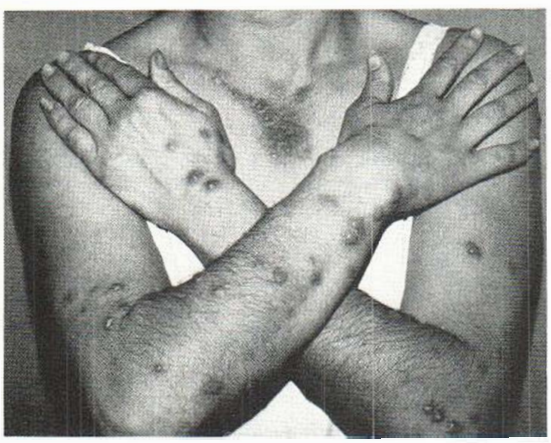

Fig. 1. Polymorphous cutaneous eruption with herpetiform lesions.

Laboratory data

Results of laboratory test carried out several times during the active phase of the illness and including blood counts, immunoglobulin levels, antistreptolysin 0 titre, rheumatoid factor, latex agglutination test, antinuclear antibodies, urinalysis, and blood cultures were all normal or negative, with the exception of markedly elevated sedimentation rate of over 50 mm in all patients.

Histopathology. In this series biopsies of a herpetiform lesion in each patient were obtained all of them showing the same histopathological changes to a varying degree. Although a variable degree of epidermal abnormality was present in all the specimens, the most important abnormalities affected the dermis. In addition to a constant hypogranulosis, the epidermal changes included varying degrees of intercellular and intracellular edema affecting the whole epidermis (Fig. 6 A). In 2 cases the epidermal edema was so severe as to produce intra-epidermal vesiculation and formation of bullae (Fig. 4). Focal or generalized epidermal necrosis was always absent, but individually necrotic keratinocytes ("eosinophilic bodies") into the lower epidermal layers were observed in two specimens (Fig. 6 A). Small focal areas of vacuolar alteration at the dermo-epidermal interface were seen in 2 cases.

Severe papillary edema with a significant underlying inflammatory infiltrate was the most striking finding among the dermal changes (Fig. 5). In several specimens intradermal pressure bulla formation resulting from severe papillary edema was observed.

An important nodular perivascular infiltrate was seen in all cases. In most of them it was so pronounced as to form a band-like infiltrate at the base of subepidermal bulla. The infiltrate consisted of mononuclear cells such as lymphocytes and histiocytes, with only a few neutrophils and variable amounts of nuclear dust ranging from middle to severe (Fig. 6 B). The mononuclear cells predominated in

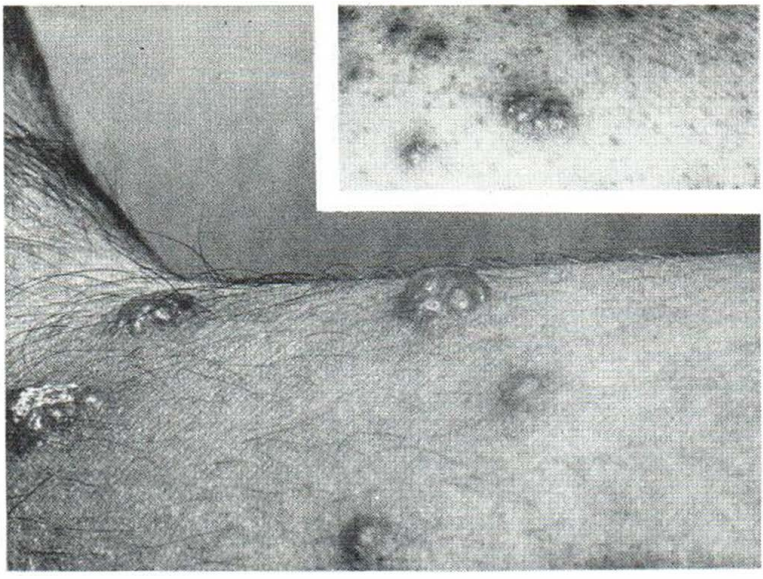

Fig. 2. Herpetiform lesions resulting in multilocular blisters. Inset: early herpetiform lesion.

all the specimens except in those showing intra-epidermal vesiculation.

Dilated capillaries and endothelial swelling were the only vascular changes found in most specimens. Specific signs of vasculitis or extravasation of erythrocytes were not seen. Direct immunofluorescent examination of involved skin performed in two specimens was negative.

DISCUSSION

Classically, the cutaneous manifestations observed in EM are classified into two groups, with numerous transitional forms (9): an erythemato-papular type and a vesiculo-bullous type with typical iris and target lesions, usually accompanied by involvement of the mucous membranes. Both types may be observed in the same patient.

Histologically, a dermal and epidermal type of EM has been described recently (5), with bulla formation taking place at a different location in each type, as had been reported in previous ultrastructural studies (3, 4, 12, 13). In all our patients the cutaneous eruption were extremely alike, as were the histological findings. We think that the fever, the elevated ESR, the occurrence of different morphological forms of lesions, the acute and self-limited course and the consistent histological find-

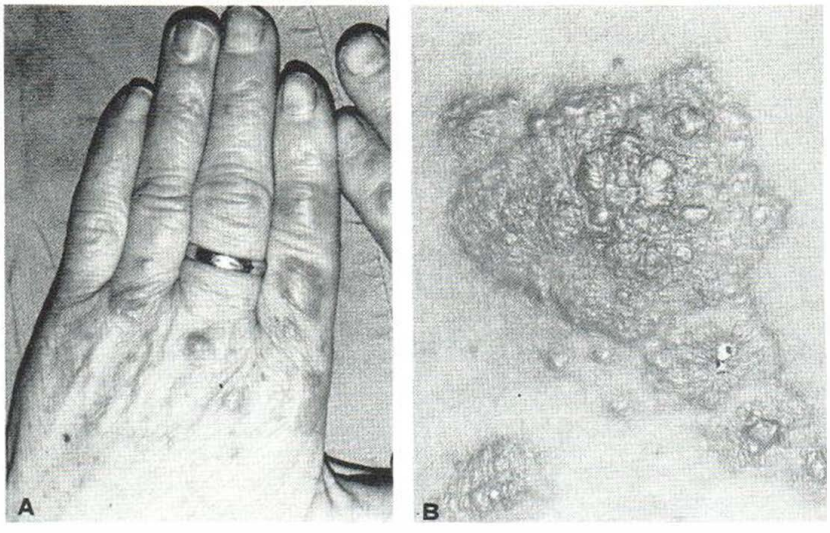

Fig. 3. (A) urticarial plaque, and (B) raised erythematous plaque on the V area of the upper chest resembling the cutaneous lerions of Sweet's Syndrome.

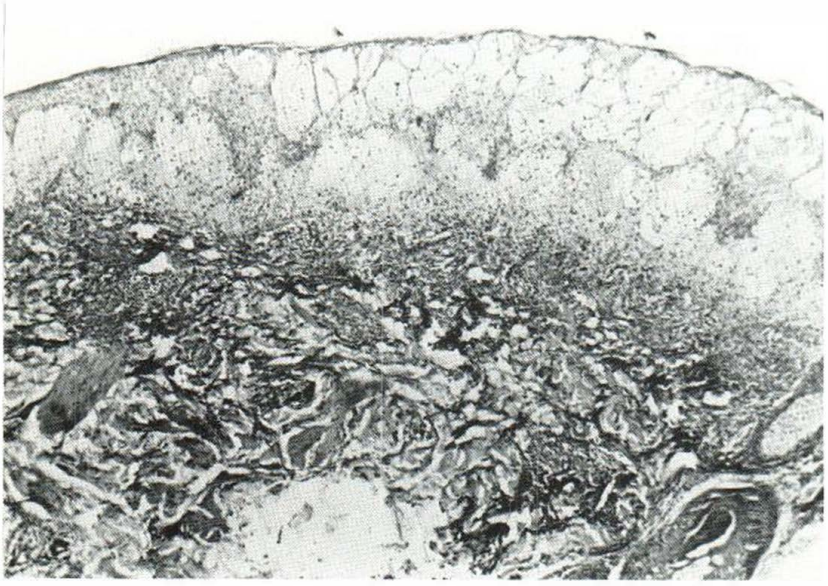

Fig. 4. Section from a herpetiform lesion exhibiting severe intra-epidermal vesiculation, papillary edema and dermal inflammation (H-E, 54).

ings-all support the diagnosis of erythema multiforme. However, several facts must be pointed out.

In spite of the polymorphous appearance of the cutaneous eruption in our patients, the characteristic lesions called by us 'herpetiform' were the only ones always present in all of them, located mainly on the dorsum of the arms and forearms. To our knowledge this has not been described previously and gives this cutaneous eruption a distinctive appearance. Typical iris and target lesions and involvement of the mucous membranes were not observed in any of our cases.

Histologically, although mainly of dermal type, all our patients showed features of both dermal and epidermal types of EM in one and the same lesion, even with intra-epidermal and subepidermal blister formation in 2 cases. Thus, a clear distinction be-

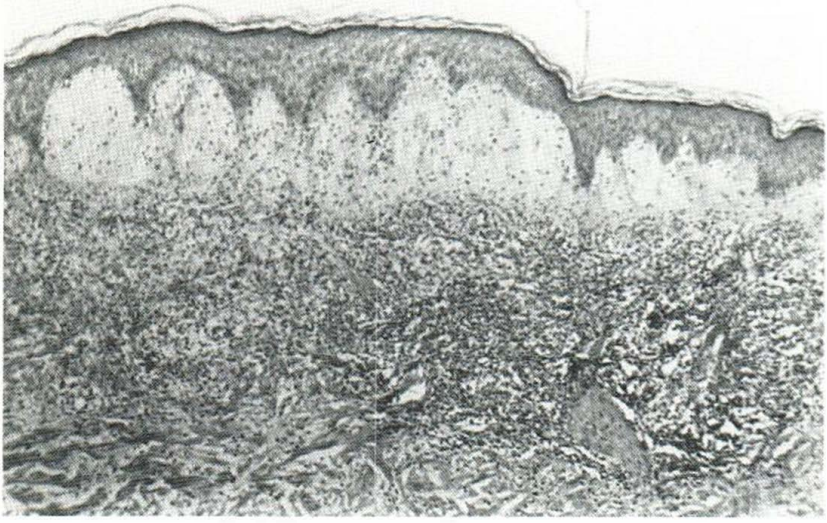

Fig. 5. Section from a herpetiform lesion showing a predominantly dermal disturbance in the form of severe papillary edema with underlying inflammatory infiltrate. Intercellular and intracellular epidermal edema is also present (H-E, ×54).

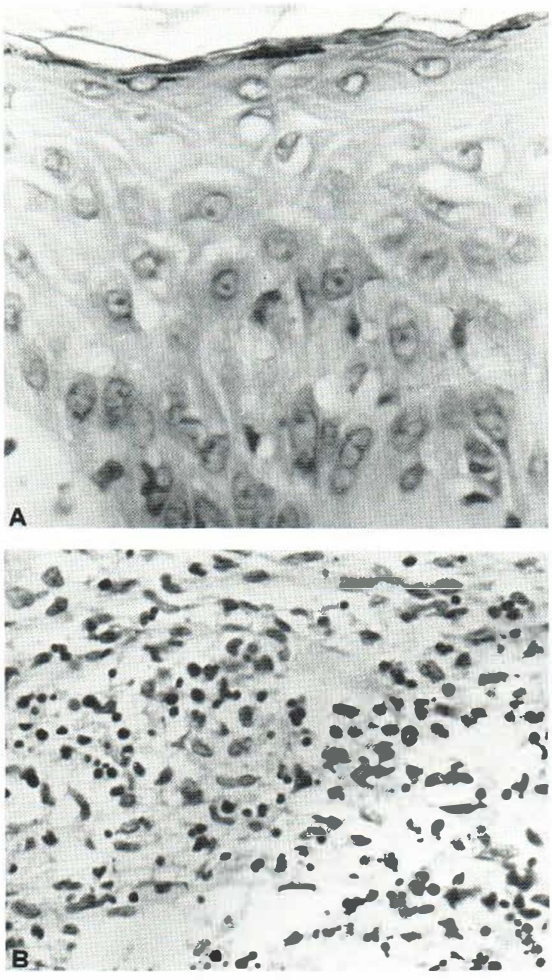

Fig. 6. (A) Detail of Fig. 5 showing the intracellular and intercellular epidermal edema and some individually necrotic keratinocytes (H-E, 360). (B) Detail of Fig. 5 exhibiting the dermal infiltrate consisting of mononuclear round cells and nuclear dust (H-E, 144).

tween dermal and epidermal types of EM (11) cannot always be made. A distinctive feature in all these cases, that casts some doubt on the diagnosis of EM, was the nature of the dermal infiltrate consisting of mononuclear cells intermingled with very scanty neutrophils and a variable amount of nuclear dust ranging from moderate to severe. The dermal infiltrate in EM is usually lymphohistiocytic, and is sometimes eosinophils present in significant quantities (2). Some authors (1) consider that neutrophils and nuclear dust are always absent from the dermal infiltrate of EM, whilst others (11) consider that they can be present, although only rarely.

For the differential diagnosis of our cases, leukocytoclastic vasculitis and Sweet's syndrome must be considered. The lack of specific signs of vasculitis such as fibrinoid necrosis or vascular wall derangement, rule out the diagnosis of leukocytoclastic vasculitis.

Some of the cutaneous lesions of our patients, such as the raised plaques located on the face and V area of the upper chest, are similar to the cutaneous lesions of Sweet's syndrome, but bullous lesions do not occur in Sweet's syndrome (5, 7, 14) and none of our cases showed peripheral neutrophil polymorphonuclear leukocytosis, a common feature of Sweet's syndrome. Furthermore the leukocytoclasis without vasculitis and papillary dermal edema observed in all our patients are common histological findings in Sweet's syndrome, but all of them showed severe epidermal abnormalities, while the epidermis in Sweet's syndrome has usually been reported to be normal (15) although some isolated cases have been reported showing intra-epidermal vesiculation (6, 10). Hence, in spite of the debated relationship between EM and Sweet's syndrome (8), we think that the diagnosis of Sweet's syndrome may be ruled out. Finally, the morphology of the cutaneous lesions, histopathological findings, laboratory data and clinical course differentiate our cases from other forms of bullous or erythematous eruptions such as dermatitis herpetiformis, pemphigoid and lupus erythematosus, and the lack of previous drug intake excluded a drug eruption.

We conclude that our patients showed a special form of EM which differs from the classical form of EM by the presence of the cutaneous lesions called by us 'herpetiform' showing a histopathological picture of dermal and epidermal type of EM but with leukocytoclasis, the age of the patients, the higher incidence in females, the prodromal period suggesting an infective process and the lack of involvement of the mucous membranes, in spite of the severe cutaneous involvement.

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