

## The Dermal Type of Erythema Multiforme: A Rare Variant of Stevens-Johnson Syndrome or Cases of Clinical Misclassification?

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Since 01.04.90 the Dokumentationszentrum schwerer Hautreaktionen (dZh) in Freiburg has registered cases of severe skin reactions like erythema exsudativum multiforme majus, Stevens-Johnson syndrome and toxic epidermal necrolysis in Germany. With the largest study so far of histological slides from patients included in this registry we were able to show that the epidermal type of erythema multiforme described by Orfanos et al. is the histopathological correlate of these severe skin reactions. Except two biopsies all of the specimens taken from the registered patients showed histological characteristics of this type of erythema multiforme.

These two cases are now reported. Clinical data and photographic documentation did not prove authentic erythema multiforme. The lesions of both patients were described as atypical macules and papules; mucosal sites were only locally involved. Biopsies taken from the patients had the characteristics of the dermal type of erythema multiforme (Orfanos et al.).

We conclude that histomorphological characteristics of the dermal type, in addition to an atypical clinical course, favour another diagnosis, such as multiforme-like eruption. *Key words:* histopathology; erythema exsudativum multiforme majus; epidermal type; multiforme-like skin eruptions.

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Erythema exsudativum multiforme majus (EEMM), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are often summarized as erythema multiforme (1). Orfanos et al. (2) described two histological types of erythema multiforme. The epidermal type shows epidermal necrosis up to necrolysis with subepidermal vesiculation, no significant papillary oedema and a sparse, mostly perivascular spotted dermal infiltration of lymphocytes. Most of these specimens derived from typical target lesions. The dermal type is characterized by extensive dermal oedema with some vacuolar alteration of the keratinocytes at the epidermal-dermal junction. In addition, an infiltration of lymphocytes and histiocytes can be found in the upper dermis. Epidermal necrosis is hardly seen. Clinically macular and papular lesions were described.

From the German registry of severe skin reactions (Dokumentationszentrum schwerer Hautreaktionen, dZh) 149 skin biopsies were reviewed in order to investigate how often these two types of erythema multiforme were present (3). All cases were classified according to an internationally elaborated consensus definition of severe skin reactions, which is based on the morphology of lesions, their distribution and the extent of blisters and erosions related to the body surface area (BSA) (4). In this largest histopathological study so far only one case

clinically classified as SJS could be found that fulfilled the histological criteria of the dermal type of erythema multiforme. After critically reviewing this case we concluded that anamnestic exploration as well as clinical description of the skin lesions did not prove typical erythema multiforme. We found another case which was excluded from the study at first sight, but showed similar features in terms of clinical picture and histopathological alterations. Both cases are reported here.

### CASE REPORTS

#### Case 1

On 26.01.92 a 58-year-old woman was admitted to a municipal hospital with the diagnosis of a severe skin reaction. The patient presented with generalized erythematous raised atypical targets and small blisters in the centre of these lesions. The extent of blisters and erosions was less than 10%; exanthema covered about 80% of the BSA. Only on the nasal and oral mucosa were small blisters. Nikolski's sign was negative. Anamnestic exploration revealed malaise, sore throat, cough, nausea and fever of 39°C a few days before.

At the date of hospitalization the patient took the following four drugs: Euthyrox<sup>®</sup> (levothyroxine-Na, indication: thyroidectomy because of adenoma, intake for 17 years), Concor<sup>®</sup> (bisoprolol fumarate, indication: hypertension, intake for 28 years), Aponal<sup>®</sup> (doxepin, indication: sleep disorder, intake for 7 years) and Gastrosil<sup>®</sup> (metoclopramid-HCl, indication: nausea, intake for 16 years).

Laboratory data did not prove an acute infection of yersinia or mycobacteria, and rheumatoid factors were also negative. The haemogram and blood counts showed no pathological findings except a temporary leukocytosis on 27.01.92 (count: 16,500 c/μl). An ENT-consultation revealed a chronic tonsillitis. A skin biopsy from this patient was performed on 28.01.92 and showed a thin hyperkeratotic epidermis with regular layers and extensive dermal oedema below. In the upper dermis a sparse superficial perivascular infiltration containing lymphocytes and histiocytes could be seen. Diagnosis: dermal type of erythema multiforme.

On the day of admission medication was removed because the diagnosis of drug-induced EEM was suspected. The patient was treated initially with Decortin H<sup>®</sup> 80 mg (prednisolone). Later the dosage was reduced. Topical treatment contained Lotio zinci and Cold Cream<sup>®</sup>.

The vesiculae dried without epidermal peeling. All lesions healed without sequelae. When the patient was discharged, Adalat retard<sup>®</sup> (nifedipine) was started because of hypertension. This case was initially evaluated as a "probable" case of SJS according to the criteria published by Bastuji-Garin et al. (4).

#### Case 2

On 07.12.92 a 69-year-old woman was referred to a department of dermatology with the diagnosis of EEM made by her family physician. At the time of her admission confluent erythematous atypical target lesions, partially with a bullous centre, could be seen mainly on her trunk. Only the oral mucosa was slightly erosive. The patient had been taking only one drug until 06.12.92: Betasamid<sup>®</sup> (penbutololsulfat, furosemid, indication: hypertension).

Pathological blood counts (08.12.92): uric acid 7.3 mg/dl, ferrum 23 μg/dl, albumin 58.2%; alpha-1 and beta-globulins were increased



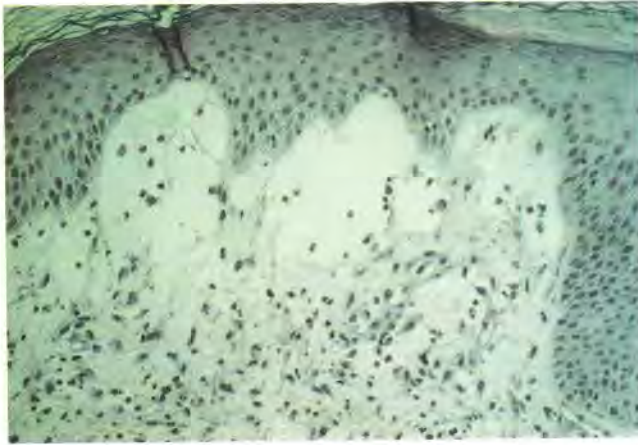


Fig. 1. Histopathological specimen from patient 2. Epidermal structures are not involved. Over the epidermis a crust of fibrin can be seen. Below there is dermal oedema. In the upper dermis a perivascular inflammatory infiltration of eosinophils and lymphocytes is evident. Diagnosis: dermal type of erythema multiforme (hematoxylin-eosin,  $\times 50$ ).

with 5.4% and 14.8%. Fructosamin was low with 175  $\mu\text{mol/l}$ . Haemograms (08.12. and 14.12.92) showed hypereosinophilia with 29%, and low monocytes and lymphocytes with 1% and 15%, respectively. Blood tests and smears did not prove acute bacterial, viral or mycotic infections. Total IgE was  $>2,000$  kU/l; SX1 (blood test to prove antibodies against common inhalative antigens, e.g. cathair, mites etc.) was positive. A general medical examination did not show any pathological findings. A biopsy taken from the left forearm on 09.12.92 had the characteristics of the so called dermal type of erythema multiforme (Fig. 1).

Initially the patient was treated with Urbason<sup>®</sup> tablets (methylprednisolone, dosage: 240 mg daily), Gelusil liquid<sup>®</sup> (aluminium-magnesium-silicathydrat) and Tavegil<sup>®</sup> tablets (clemastinhydrogenfumarat). Betasemid was removed during hospitalization. Topical therapy contained 0.5% Eosin, Volon-A-Schüttelmixtur<sup>®</sup> (triamcinolone), Thesit 3% (polydocanol) and Solutio Castellani cum colore. There was a rapid improvement that allowed the patient to be discharged on 30.12.92.

## DISCUSSION

The reported cases had the following features in common: atypical target-like lesions with small vesicles in the centre especially on the trunk, partly non-haemorrhagic oral lesions and histological features of the so called dermal type of erythema multiforme. In addition, both patients took a  $\beta$ -sympatholytic substance (penbutololsulfat, bisoprololfumarat). Beta-receptor antagonists can cause skin reactions, although skin eruptions after long-term antihypertensive therapy are rarely seen (5). Routine laboratory findings did not reveal pathological findings of acute infections or visceral involvement.

The atypical clinical description for EEMM, SJS and TEN suggests that differential diagnoses should be discussed. Often generalized drug eruptions show macular or papular exanthema, which could at least imitate target-like lesions (6). Extensive mucosal involvement is rarely seen in allergic drug rashes (1, 6). Cases of severe skin reactions according to Bastuji-Garin et al. (4) show either erosions and blisters of more than 10% of the BSA or target-like lesions with haemorrhagic-erosive mucosal involvement.

The histopathological diagnosis of the dermal type of erythema multiforme is questionable because of similar features compared to bullous and multiforme-like drug eruptions (2, 6). Urticarial or vesiculobullous allergic eruptions have a lack of necrotic keratinocytes within the epidermis. Only few keratinocytes at the epidermal-dermal junction present with vacuolar alteration. In addition, a remarkable oedema in the upper dermis is seen beside a sparse and mostly perivascular spotted infiltration of lymphocytes, histiocytes and a few eosinophils (6).

Côté et al. (7) found the dermal type in 2 of 15 biopsies taken from patients with SJS. In contrast, no specimen from a patient with EEMM showed the characteristics of this type of erythema multiforme. These findings might point to special histopathological features of SJS.

Another possibility is that the histomorphological changes of the dermal type correlate to a certain state of development of EEMM, SJS or TEN, although Ackerman et al. (8) did not describe a stage where extensive oedema and lack of epidermal necrosis in erythema multiforme are present. Sequential histological specimens taken from patients with SJS might evaluate these findings. Unfortunately, examinations of the frequency of biopsies proved that the clinical diagnosis of SJS is often not confirmed by histological evaluation (3).

We are certain that the so called epidermal type of erythema multiforme is the real histological correlate of EEMM, SJS and TEN according to the classification of Bastuji-Garin et al. (4). This hypothesis (3) is supported by the reports of Ackerman et al. (8) and Bedi & Pinkus (9), who had also seen similar histological alterations in biopsies of patients with erythema multiforme. The histomorphological characteristics described by these authors were not different from the features of the epidermal type.

We therefore propose the diagnosis of a more benign multiforme-like drug eruption in cases with histopathological characteristics of the dermal type of erythema multiforme described by Orfanos et al. (2). These cases are not compatible with genuine erythema multiforme.

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