Pemphigus erythematosus: Clinical and Histo-immunological Studies in Two Unusual Cases

TH. V. JOOST,[1] E. STOLZ,[1] F. B. BLOG,[1]
F. TEN KATE[2] and V. D. VUZEVSKI[2]

[1]*Department of Dermato-Venereology and* [2]*Department of Clinical Pathology, University Hospital Dijkzigt, Erasmus University, Rotterdam, The Netherlands*

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In two unusual cases of pemphigus, classified as pemphigus erythematosus (PE), the clinical and laboratory data are summarized and discussed. In case I, with characteristic immunologic features of PE, acantholysis was detectable only by the EM-technique. Case II with transitory pemphigus and features of SLE was diagnosed as "probable PE". In this case (case II) concomitant incidence was found of benign thymoma. In addition in both cases the patterns of T-cells- and T-cell-subsets in blood and lesional skin are briefly discussed. *Key words*: *Pemphigus*; *Lupus erythematosus*; *Thymoma*; *T-cell phenotypes*; *Electronmicroscopy*. (Received October 5, 1983.)

Th. v. Joost, Department of Dermato-Venereology, Academisch Ziekenhuis Rotterdam/ Dijkzigt, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands.

In pemphigus erythematosus (PE) (Senear-Usher syndrome) different possibilities are discussed with respect to the classification: variety of pemphigus or of LE or a syntropy of both diseases. Based on immunofluorescence (IF) data in particular the disease apparently represents a combination of pemphigus and LE (1, 2).

In this report two rather unusual cases classified as PE are described.

CASE REPORTS

Case I

A 68 year old female had a erythemato-squamous facial rash and similar skin lesions on the trunk resembling pemphigus seborrhoicus. Clinically no superficial blistering was noted. Sunlight appeared to be an evident luxating factor in the patient. Relation with drugs could not be established.

Histologic and direct IF-studies. Routine light microscopy (LM) and direct IF-study (DIF) of lesional skin revealed features comparable with those in discoid LE: focal hyperkeratosis, slight atrophy of the Malphigian layer and slight degeneration of the basal membrane (BM) (PAS-staining), but acantholysis could not be shown. In the dermis, in particular perivascular and to lesser extent in the upper dermis a predominantly mononuclear infiltrate was present, with epidermal invasion of mononuclears focally. Granular deposits of IgG and complement were noted at the Bm-zone. Repeated LM-examination of new lesions and of older lesions of the trunk revealed only a slight broadening of the higher epidermal intercellular regions, but no acantholysis. In the basal cell layers of some biopsies conspicuous intercellular edema was noted. By DIF-staining conspicuous homogenous deposition of IgG was seen intercellularly in the upper epidermal regions, but complement was negative at this site. Moderate deposition of IgG and complement (C3) was however seen at the Bm-zone.

In normal appearing skin the DIF was negative. Of interest is that subsequent electronmicroscopic (EM)-study, performed in the epidermal regions where acantholysis was expected, revealed the typical features for initial acantholytic blister formation: absence of desmosomes, lacunes intercellularly and peninuclear configuration of the tonofilaments (Fig. 1).

Additional immunologic data. Indirect IF-study revealed high titer (1:640) pemphigus antibodies (guinea pig lip as substrate). Auto-antibodies were also found to other substrates: thyreoid, parietal cells and skeletal muscle. DNA-antibodies and LE-cells were absent. HLA-antigens: A 28, AW 32, BW 44, BW 60 and CW 3. Peripheral B-cells: 8%.

In this study (case I and II) the methods and materials for detection of T-cell-subsets in the blood by

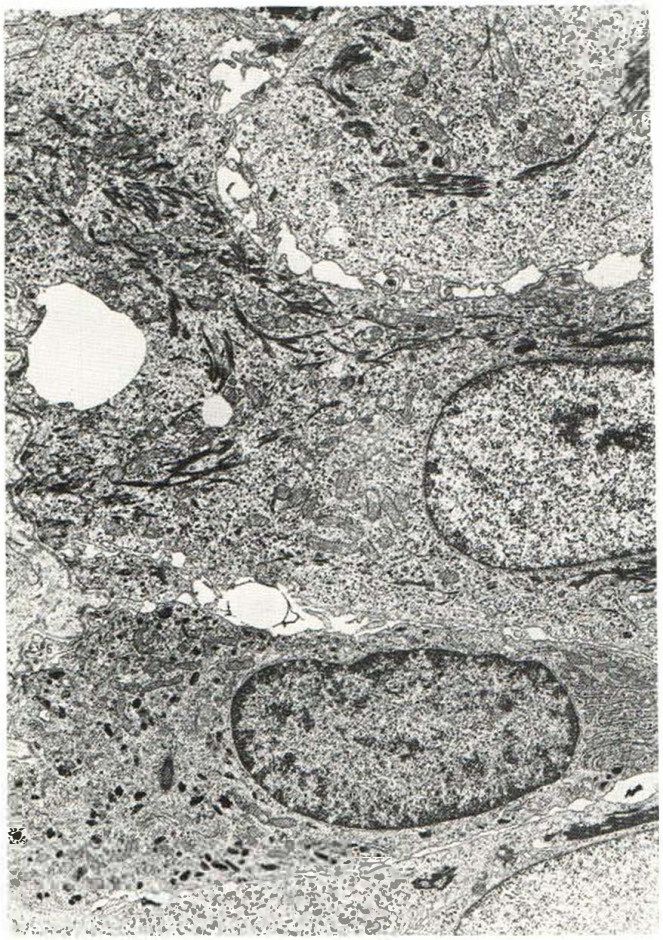

Fig. 1. Case I: EM-method (lesion on the trunk): Characteristic features for acantholysis are detectable: desmosomes are absent; intercellular clefts are present; perinuclear centralization of tonofillaments (×29 000).

monoclonal antibodies, referred as OKT-series, were used as described recently by Foon et al. (3). For the detection of surface antigens of T-cells in the tissue immunoperoxydase procedures using monoclonal antibodies, referred as Leu-series, were used (4). Monoclonals used, were: OKT 3, Leu 1 (reactive to pan-T lymphocytes), OKT 4, Leu 3a (reactive to helper-T-lymphocytes) and OKT 8, Leu 2a (reactive to suppressor/cytotoxic-T-lymphocyte). In the peripheral blood (Case I) were found OKT 3^+: 71% (n.v.: 50–80%), OKT 4^+: 47% (n.v.: 30–48%), OKT 8^+: 15% (n.v.: 20–32%).

Both Leu 2a and Leu 3a bearing T-cells were seen especially in dermal and to less extent in epidermal regions. Predominantly helper-T-cells were however detected at these sites.

Based on the IF- and EM data in particular this case was classified as PE. Myasthenia gravis and/or thymoma were not found in this patient. By oral prednison (100 mg daily) most but not all lesions disappeared, inspite of additional topical treatment with corticosteriods. Oral prednison was then gradually decreased to 50 mg daily. Because of the favourable effect of thalidomide in cases of discoid LE as described recently (5), in addition oral thalidomide (dose: 200 mg daily) was given.

Four weeks here-after all lesions were healed. Thalidomide therapy was stopped and the prednison dosis was gradually decreased to 10 mg daily. At that time pemphigus antibodies were however still detectable (titer 1 : 320).

Case II

A 68-year-old man had a rash restricted to the trunk and the upper arms existing for about two weeks before hospitalization. Physical examination revealed multiple erythemato-crustous patches with focally superficial blisting. The Nikolsky-phenomenon was positive. Before the development of lesions the patient was in good health. No drugs were used.

Histologic and direct IF-studies. LM-examination of the skin revealed clearly acantholysis in the upper epidermis. The PAS-staining of the Bm-zone was normal. In the dermis a mixed infiltrate but predominantly existing of mononuclear cells were seen diffusely in the upper dermis and in less extent focally around the blood vessels. Focal infiltration of mononuclear cells was present in the epidermis. IgG and complement (C3) were clearly shown together intercellularly in the upper epidermis. IgG and C3 were absent at the dermal-epidermal junction.

Additional immunologic data. Circulating pemphigus antibodies were absent in this patient. Anti-DNA antibodies, LE-cells and smooth-muscle antibodies were however present in the serum. HLA-antigens: A 2, A 3, BW 62, BW 35, CW 3 and CW 4. Peripheral B-cells: 12%. The data of the peripheral T-cell differentiation (OKT-battery) were: OKT 3^+: 85%, OKT 4^+: 57%, OKT 8^+: 35%. In case II, using monoclonal Leu-series a partly different pattern of T-cell-subsets was seen in lesional skin in comparison to case I. Focally moderate infiltrates of helper-T-cells in the epidermis were seen, Leu 2a-bearing T-cells being absent at this site.

In this patient (II) the data were compatible with the association of pemphigus of the foliaceus type with serological features of SLE (anti-DNA antibodies and LE-cells). Routine X-ray examination and additional histopathologic examination revealed the presence of a benign thymoma.

Clinical signs of myasthenia gravis were not found in this patient. The impression was gained that thymoma preceded the skin lesions. No objective and subjective signs of compression in the chest occurred in the patient. Because of uncertainty with regard to the exact nature of the tumor, initially no immunosuppressive therapy was given. The lesions however diminished spontaneously and four weeks after hospitalization the lesions had disappeared, control by corticosteroids being not necessary.

DISCUSSION

It might be considered that in case II a foliaceus type of pemphigus was associated casually with SLE. This because it might be argued that if PE is a real syntropy of LE and pemphigus, features of both diseases should be reflected histologically and immunologically in the skin lesions. Otherwise in auto-immune syndromes an overlap of immunologic phenomena frequently occurs and sometimes a sharply defined classification seems to be hazardous. In case II, LE-cells and DNA-antibodies were found and thus concomitantly true features for both diseases i.e. pemphigus and SLE were present in one patient. Therefore we are inclined to consider this case as "probable PE". Of interest in case I is that only on ultrastructural level typical features for acantholysis were detectable (Fig. 1). Therefore EM-investigations must be considered in certain cases that are difficult to classify. Data in favour of a primary pathogenic role in pemphigus for respectively antibodies or for complement are reported (6). The absence of intercellular complement (C3) in this particular case (I), might possibly provide an explanation for the limitation of acantholysis if complement really has an important role in tissue injury. Of note is that the IC-antibody titer (animal-substrate) did not correlate with clinical activity in case I. In the vast majority of cases of PE systemic immunosuppressive treatment is necessary to control the disease (2). In case II, however, the skin lesions were of an unusual transitory type and healed spontaneously within six weeks. The relevant data of cases described in the world-literature of pemphigus associated with thymoma and myasthenia gravis were recently reviewed (2). It can be concluded here that only six cases of PE associated with benign thymoma were reported until now in the world-literature. In these six cases, except in one (Uhlin et al.) (7), association was seen with myasthenia (2). In case II, described here, skeletal muscle auto-antibodies were not detectable, neither clinical signs of myasthenia were found. In contrast to the case described by Uhlin et al. (7), our patient (case II) had no serum pemphigus antibodies and use of systemic corticosteroids was not necessary to control the disease and therefore this case must be considered as unique.

It is suggested that a primer defect in T-cell-suppression function might possible allow unrestrained production of auto-antibodies (8). An identical mechanism might be operative in pemphigus (6, 2).

In case I in the blood the helper/suppressor (T4/T8)-ratio was: 3.7 (47%/15%).

This ratio-value is comparable with that found in active cases of SLE and might suggest a deficiency of immunosuppressive T-cells (8). In case II the T4/T8-ratio was 1.6 and this value was considered to be normal. Maize et al. (9) suggested a relationship in pemphigus as well as in thymoma with deficiency of suppressor-T-cell function. Such a relationship however could not be established in case II. The predominance of helper-T-cells found in the skin in the two cases described here is also reported in other skin conditions (10). Two partly different patterns of T-cells were seen. These two patterns (Leu 2a and Leu 3a) probably provide only a momentary insight into the variations of T-cell-phenotype composition. In case II, T-helper-cells (Leu 3a) were present more diffusely in the upper dermis and were in particular also found in the epidermal regions. (Suppressor/cytotoxic-T-cells were however seen only in dermal regions. This finding might be compatible with the concept that in pemphigus epidermal auto-immunogens might induce helper-T-cells stimulation "in situ", reflecting the first part of the inductive limb of auto-immune response. Further longitudinal studies by use of monoclonal antibody essays are required for a better insight of T-cell-function in the auto-antigenprocessing mechanisms in bullous- and non bullous auto-immunity of the skin.

It can be concluded that the data of the cases described are different from each other, but in certain aspects also from the cases of PE reported in the literature (2).

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