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A Patient with Immunological Features of Paraneoplastic Pemphigus in the Absence of a Detectable Malignancy

Anna Verrini[1], Guiseppe Cannata[2], Emanuele Cozzani[1], Michela Terracini[3], Aurora Parodi[1] and Alfredo Rebora[1]*
[1]*Di.S.E.M Section of Dermatology, University of Genoa, Viale Benedetto XV n. 7, IT-16132 Genoa, Italy,* [2]*Costa Raniera Hospital, Department of Dermatology, Imperia, and* [3]*Laboratory of Molecular and Cell Biology, Istituto Dermopatico dell'Immacolata IRCCS, Rome, Italy. *E-mail: rebdermo@unige.it*
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Sir,

The diagnostic criteria of paraneoplastic pemphigus (PNP) include a specific serology with circulating antibodies directed to an antigenic complex consisting of plectin (>400 kDa), desmoplakin I (250 kDa), bullous pemphigoid antigen 1 (BP Ag 230 kDa), envoplakin-desmoplakin II (210 kDa) and periplakin (190 kDa). In addition, PNP antibodies may react with recombinant desmoglein 3 and with a 170 kDa protein, detected by immunoprecipitation and regarded initially as a degradation product (1). Antibodies to the 170 kDa molecule have been found more recently in almost all PNP sera (2), suggesting that they may play an important pathogenetic role (3) in the disease.

We describe here a patient with clinical, histological and direct immunofluorescence (DIF) features of PNP, but lacking a detectable neoplasm and with antibodies immunoprecipitating only the 170 and 210 kDa antigens.

CASE REPORT

A 70-year-old man with a history of alcohol abuse presented with mucosal erosions and a bullous eruption of the trunk of 1-month duration. Clinical examination revealed erosions in the oral cavity, partially covered by a creamy material. The glans penis appeared oedematous with multiple painful erosions. An acute purulent conjunctivitis and some erythematous target-like bullae on the upper chest and legs were present. Erosions extended also to the pharynx and larynx.

Laboratory tests showed only an increased erythrocyte sedimentation rate (40 mm/h) and moderately high levels of cholesterol and triglycerides (230 mg/dl and 167 mg/dl, normal values <200 and <160 mg/dl, respectively). Other routine laboratory tests were within normal limits. Histopathology of 2 biopsies, one from the oral cavity and one from the right clavicular area, showed basal acantholysis and some necrotic keratinocytes. DIF disclosed IgG and C3 deposits in the intercellular substance of epidermis and granular deposits of C3 at the dermo/epidermal junction. Indirect immunofluorescence (IIF) with monkey oesophagus as substrate showed IgG directed to the cytoplasm of the basal cells. IIF with rat bladder as substrate showed IgG antibodies directed to the intercellular substance of the epithelium. Immunoblotting analysis using cultured keratinocytes as source of antigens was performed as described elsewhere (4) and showed 3 bands at 200, 170 and 120 kDa. Immunoenzymatic tests did not show serum antibodies directed to Desmoglein 1 and 3. Immunoprecipitation, done as reported elsewhere (5), showed antibodies to the molecules of 170 and 210 kDa (Fig. 1).

Because of the clinical, histological and immuno-

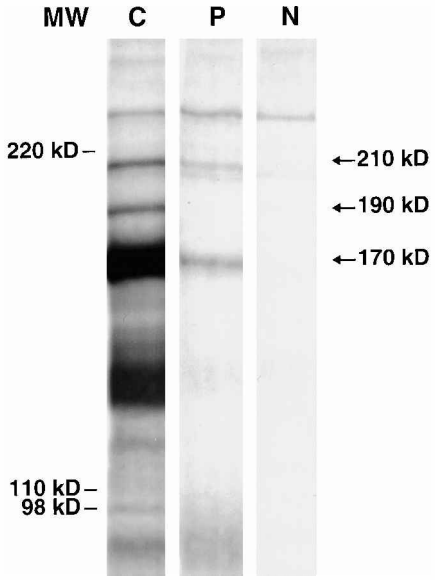

Fig. 1. Immunoprecipitation of ^{35}S-labelled human keratinocyte extracts by patient and control sera. Patient serum reacts with two antigen bands at 210 and 170 kDa (arrows). A band at 190 kDa is seen in the positive control serum and absent in patient serum. C: positive control from a patient with known paraneoplastic pemphigus; P: patient serum; N: normal human serum; MW: molecular weight standards.

pathological findings, PNP was diagnosed and the tumour was looked for. Tumoral markers such as CEA, α-FP, PSA, CA-19.9 were within normal limits. Echography of the superior abdomen and pelvis showed only a chronic hepatopathy with steatosis. A chest radiogram was negative. A colonoscopy was done because of blood in the stools and disclosed 3 colonic polyps with low, moderate and severe dysplasia, respectively.

The patient was then given 100 mg/day prednisone plus 100 mg/day azathioprine and his lesions improved slightly. Computerized axial total body scanning was planned, but could not be done because the patient suddenly died from a stroke. Permission for autopsy was not granted.

DISCUSSION

Since its original description (1), PNP has been repeatedly reported and is now considered a heterogeneous entity displaying a spectrum of at least 5 different clinical and immunopathological variants: pemphigus-like, pemphigoid-like, erythema multiforme-like, graft-vs.-host disease-like and lichen planus-like (6). A pustular form has also been described (7). Serology includes antibodies directed to an antigenic complex consisting of plectin, desmoplakin I, bullous pemphigoid antigen 1, envoplakin and desmoplakin II, periplakin and other less specific molecules.

Among the last ones mentioned, of particular interest is a keratinocyte polypeptide with a molecular weight of 170 kDa, a putative transmembranal autoantigen, which can be found in 96% of cases (3). This is the only antigen of the PNP complex with a cell surface domain and it is abundant on the cell surface in high Ca^{++} concentration cultures. For this reason it is thought to be crucial in the pathophysiology of tissue injury in PNP.

In order to confirm the PNP diagnosis, at least 2 of the target antigens must be identified (8). In our patient, since antibodies to the 2 antigens of 170 and 210 kDa were disclosed, the patient can therefore be diagnosed as having PNP. In addition, our patient had clinical DIF and IIF findings consistent with erythema multiforme-like PNP.

Conversely, pemphigus vulgaris (PV) was ruled out because in DIF our patient disclosed also C3 granular deposits at the dermoepidermal junction that are not typical of PV, in IIF on monkey oesophagus, antibodies to basal cell cytoplasm and in IIF on rat bladder, antibodies directed to the intercellular substance that are absent in PV. In addition, no anti-desmoglein 3 antibodies were detected by immunoblot analysis, immunoenzymatic tests and immunoprecipitation. Stevens-Johnson syndrome, which could be suggested by the clinical features and some immunopathological findings, was ruled out owing to the presence in DIF of IgG and C3 deposits in the intercellular spaces of the epidermis.

The absence of a known malignancy is not new in PNP. Ostezan et al. (9) reported this in a patient whose serum disclosed antibodies to a complex of antigens of 250, 230, 210 and 190 kDa. Our patient had a colonic polyp with severe dysplasia. It is recognized that about 27% of such polyps evolve to carcinoma. Whether PNP heralds such an evolution remains a matter of speculation.

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Mixed Response to Thalidomide Therapy in Adults: Two Cases of Multisystem Langerhans' Cell Histiocytosis

Gerhard Kolde, Peter Schulze and Wolfram Sterry
Department of Dermatology, Charité, Humboldt-University of Berlin, Schumannstr. 20/21, 10117 Berlin, Germany.
E-mail: gerhard.kolde@charite.de
Accepted April 23, 2002.

Sir,
Langerhans' cell histiocytosis (LCH) (formerly histiocytosis X) is a clonal disorder of proliferating histiocytic cells expressing the phenotypic markers of the epidermal antigen-presenting Langerhans' cells (1, 2). The clinical spectrum and prognosis are variable ranging from benign single-organ disease affecting single or multiple sites, to multisystem disease with involvement of two or more organs, including chronic multifocal Hand-Schüller-Christian disease and acute leukaemia-like Abt-Letterer-Siwe disease. Owing to the unpredictable and often progressive course, multisystem LCH of infants warrants therapy with prednisolone and/or cytotoxic drugs, used either alone or in combination (3). By contrast, the management of adult-onset multisystem LCH remains controversial, as the disease has a more benign character than that in infants.

Successful treatment of LCH with thalidomide was first observed in a 32-year-old woman with localized genital lesions (4). Since then, the efficacy of thalidomide has been demonstrated in several case reports (5–8). However, most of the patients treated suffered from purely cutaneous LCH. We report here on the effects of thalidomide monotherapy in two adult patients with pronounced mucocutaneous and mild visceral manifestations of the disease.

CASE REPORTS

The two patients, a 23-year-old man (patient 1) and a 61-year-old woman (patient 2), suffered from adult-onset, chronic multisystem LCH for several years. Patient 1 presented with widespread mucocutaneous lesions, with infiltration of the scalp, erythematous gum swelling, and inguinal, perianal and anal infiltration and ulceration. Patient 2 presented with a multifocal maculopapular eruption on the trunk. The visceral involvement was restricted to either a focal bone defect of the jaw (patient 1) or multifocal infiltration of the mediastinal lymph nodes (patient 2). Involvement of other organ regions and organs was ruled out after a complete physical examination, laboratory evaluation including liver function tests and phenotyping of peripheral blood mononuclear cells, abdominal and lymph node sonography, skeletal radiograph survey and computed tomography. The diagnosis of LCH was established by histological, immunohistological and electron microscopy examination of the cutaneous and visceral lesions, which showed aggregates of large histiocyte-like cells with CD1a expression and cytoplasmic Birbeck granules.

Patient 2 had previously been treated with systemic corticosteroids, which resulted in partial regression of the maculopapular skin eruption, but there was an immediate relapse after completion of the course of corticosteroid treatment.

After giving detailed information and obtaining written consent, both patients were started on thalidomide monotherapy at a dosage of 100 mg/day, which resulted in significant improvement of the mucocutaneous lesions. The maculopapular skin eruption and erythematous gum swelling resolved within one month, and the inguinal, perianal and anal infiltrations and ulcerations healed with scarring after 3 months (Fig. 1). The eroded and crusted

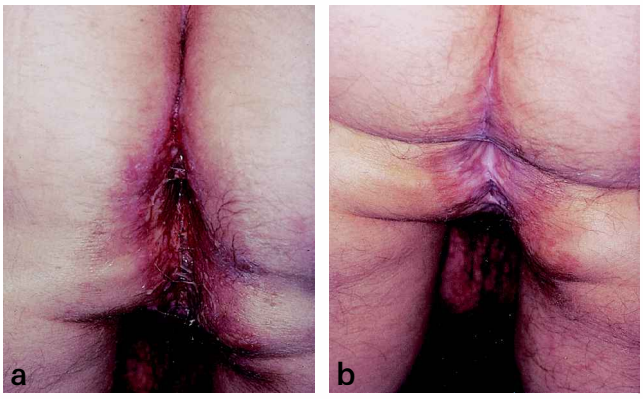

Fig. 1. Perianal and anal infiltration and ulceration (a) before and (b) after 3 months of thalidomide therapy showing healing of the lesions, with slight scarring.