

## Paraneoplastic Pemphigus Associated with Pancreatic Carcinoma

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**A case of paraneoplastic pemphigus associated with pancreatic carcinoma is presented. The histopathological and immunological features of the case, which are consistent with and differ from the accepted diagnostic criteria, are discussed. Key words: epidermal antigens; immunoblotting; Anhalt's criteria.**

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### CASE REPORT

A 59-year-old Israeli man from Southern Russia had an oral ulceration and skin rash, which had appeared after taking antibiotics for a sore throat. He had lost 20 kg in the previous year and was taking glibenclamide and metformin for non-insulin-dependent diabetes mellitus of recent onset. Examination at hospitalization revealed an obese man with a fever of 38°C, ulcers on the buccal mucosa, lips and right tonsil (Fig. 1), peeling of the palms (Fig. 2) and a generalized polymorphous skin eruption confined to the trunk with some target lesions. Cervical and inguinal lymph nodes were enlarged and there was a 10-cm mass palpated in the epigastrium. The scrotum was eroded.

Laboratory investigations yielded the following abnormal results: blood glucose 146 mg/dl (normal range 70–110), total protein 93 g/l (60–80), albumin 26 g/l (35–53), globulin 67, GOT 54 mμ/ml (7–40), GPT 23 mμ/ml (≤29), γ-GT 121 mμ/ml (<38), LDH 330 mμ/ml (160–320), alkaline phosphatase 110 mμ/ml (30–85), and leukocytosis of  $11.1 \times 10^3$ , with 15.9% lymphocytes and 11.1% eosinophils. Coagulation parameters revealed slightly increased prothrombin time, but thrombocyte count was normal. Rouleaux formations were

seen on blood smear, consistent with the hyperproteinemia described above. Immunoelectrophoresis study revealed increased levels of polyclonal IgG and IgM.

Skin cultures from the generalized skin eruption were negative for herpes simplex, but throat cultures disclosed β-hemolytic group C streptococcus. Two blood cultures showed methicillin-resistant coagulase-positive *Staphylococcus aureus*. Serologic tests were negative for herpes virus, enterovirus, CMV, EBV, HIV and VDRL.

Abdominal ultrasound prior to hospitalization revealed a mass in the body of the pancreas with retroperitoneal lymphadenopathy and signs of liver metastases. These findings were confirmed during the present hospitalization by abdominal computerized tomography and endoscopic ultrasound, which also disclosed extensive lymphadenopathy around the stomach and in the mediastinum.

Fine needle aspiration of the abdominal mass showed adenocarcinoma of the pancreas, with positive CEA and CA 19–9 on immunohistochemical staining. Fine needle aspiration also showed histological reactivity without metastases in the cervical lymph nodes. Bone marrow biopsy was refused.

Histological study of a biopsy specimen from a lesion on the patient's arm showed focal vacuolization of epidermal cells. The superficial dermis contained mild perivascular lymphocytic infiltrates, some of which focally obscured the dermo-epidermal junction.

Direct immunofluorescence studies of perilesional skin revealed granular C3 deposits in the epidermal intercellular spaces. Indirect immunofluorescence studies on monkey esophagus revealed deposition of IgG in the epidermal intercellular spaces, up to a titer of 1:640. Indirect immunofluorescence studies on rat urinary bladder were negative.

Immunoblotting with the patient's serum demonstrated immunoreactivity with 7 epidermal polypeptides of molecular weights 105 kD, 130 kD, 170 kD, 190 kD, 210 kD, 230 kD and

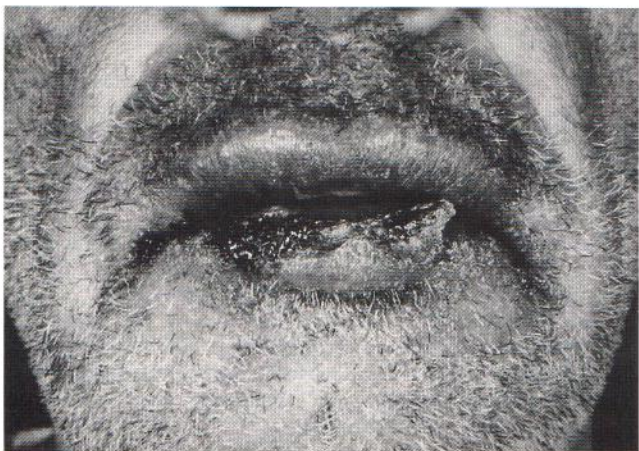


Fig. 1. Ulcers on the lips of the 59-year-old man at the time of hospitalization.



Fig. 2. Peeling of the palms at hospitalization.

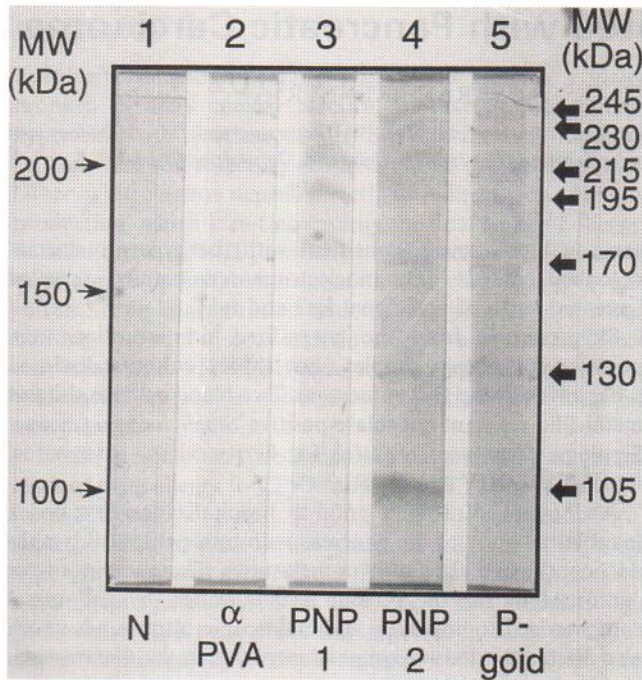


Fig. 3. Immunoblotting with the patient's serum (PNP 2), showing immunoreactivity with 7 epidermal polypeptides of varying molecular weights (MW). Other sera for purposes of comparison: N=normal, P-goid=bullous pemphigoid,  $\alpha$  PVA=affinity purified rabbit anti-130 kDa, PNP=paraneoplastic pemphigus serum.

250 kDa (Fig. 3). For this analysis, epidermal membrane extracts were separated on 7.5% acrylamide gels by sodium dodecyl sulfate polyacrylamide gel electrophoresis and transblotted onto nitrocellulose papers. Individual lanes were reacted with the sera of the paraneoplastic pemphigus (1–3).

The patient was treated with i.v. clindamycin for 6 days. Two weeks later the skin eruption had subsided but the buccal ulcers persisted. Two courses of chemotherapy and radiotherapy were administered, but the patient died 2 months later from generalized cancer.

## DISCUSSION

Paraneoplastic pemphigus was defined by Anhalt et al. in 1990 (4) as an autoimmune bullous disease that can develop in patients with various forms of neoplasia. These authors gave 5 criteria for diagnosis of the disease (4,5): 1) a polymorphous eruption affecting skin and mucous membranes, often resembling erythema multiforme; 2) histopathological features that include epidermal acantholysis and dyskeratosis with basal layer vacuolar changes (4,6); 3) intraepidermal and/or basement membrane zone deposition of IgG and C3 on direct immunofluorescence; 4) serum autoantibodies to multiple epithelia; and 5) immunoprecipitation of a unique complex of 250 kDa, 230 kDa, 210 kDa and 190 kDa antigens.

Consistent with Anhalt's criteria, our patient's skin eruption was polymorphous and resembled erythema multiforme. Histologically there was no acantholysis or dyskeratosis, but vacuolar epidermal changes were present. The histological picture was typical, with the presence of bullae. Horn &

Anhalt (6) point out that the histology is variable and may resemble a drug eruption, as was seen in our case.

Our patient met other criteria of Anhalt's, including epidermal intercellular C3 deposits in the epidermis and in the epithelium and immunoreactivity to epidermal antigens 250 kDa, 230 kDa, 210 kDa and 190 kDa. Our patient also showed immunoreactivity to 105 kDa, 130 kDa and 170 kDa. Both Anhalt et al. (4) and Hashimoto et al. (7) mention the 170 kDa protein, and the latter authors note that in recent studies nearly all paraneoplastic pemphigus sera immunoprecipitated this transmembrane molecule. These findings suggest that the 170 kDa protein might play an important role in the pathogenesis of the disease. To the best of our knowledge, our patient is the first reported case to exhibit immunoreactivity to the epidermal autoantigens 130 kDa and 105 kDa.

The clinical course in our patient corresponds with that described in the literature on paraneoplastic pemphigus. These patients respond partially and poorly to immunosuppressive therapy (8), and survival time is 1 month to 2 years, with a mean of 9 months (8).

All reported cases have been associated with a neoplasia, usually a lymphoproliferative malignancy (4, 9–14), although other malignant and benign tumours have been reported, including poorly differentiated sarcomas (4, 15), bronchogenic squamous cell carcinoma (9), Castelman's tumour (4, 12, 16) and benign thymoma (4, 17).

Our patient represents a case of paraneoplastic pemphigus. The associated pancreatic carcinoma has not been reported and can be added to the growing list of associated tumours.

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