

Paraneoplastic Pemphigus Associated with Malignant Gastrointestinal Stromal Tumour

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Sir,

Paraneoplastic pemphigus (PNP) is an autoimmune bullous disease characterized by severe mucous membrane involvement, polymorphous skin eruptions, and underlying neoplasms. Most cases are associated with lymphoproliferative neoplasms, and solid tumours have rarely been associated with PNP (1, 2). We describe here a patient with PNP associated with malignant gastrointestinal stromal tumour (GIST).

CASE REPORT

A 57-year-old woman had a 1-month history of painful erosions in the oral cavity and skin eruptions on her trunk and extremities. Physical examination revealed multiple well-demarcated erosions on the lower lip and oral mucosa, together with fine oedematous erythema on her back and extremities (Fig. 1a). Standard laboratory tests yielded normal findings, except for a slightly increased C-reactive protein level (0.68 mg/dl). The biopsy specimens taken from the erythema on the dorsum of the foot showed vacuolar interface dermatitis with scattered individual keratinocyte necrosis and perivascular lymphohistiocytic infiltration in the papillary dermis.

Her skin lesions worsened significantly during the following 6 weeks. She developed severe stomatitis, pseudomembranous conjunctivitis, and blisters on her extremities associated with fever and general fatigue (Fig. 1b). The second biopsy specimen obtained from a bullous lesion on her forearm revealed suprabasal cleft with acantholysis. Indirect immunofluorescence on normal human skin revealed cell surface staining, up to a titre of 1:160 (Fig. 1c). Enzyme-linked immunosorbent assay revealed increased antibodies against desmoglein 3 (40.03; normal <7.0), desmoglein 1 (15.96; <14.0) and bullous pemphigoid antigen 180 (104.50; <9.0). Immunoblot analysis using an ethylenediaminetetraacetic acid (EDTA)-separated human skin extract was performed as described previously (3) and revealed the presence of autoantibodies reactive with a doublet of PNP antigen, the 210-kDa envoplakin and 190-kDa periplakin (Fig. 2). In addition, the 130-kDa desmoglein 3 antibody also developed with the exacerbation. According to the clinical, histological, and immunopathological findings, a diagnosis of PNP was made.



Fig. 1. Clinical and histopathological views. (a) Well-demarcated erosions on the lower lip and tongue. (b) Bullae on the oedematous erythema of the arm. (c) Indirect immunofluorescence of patient serum on human skin demonstrating binding of IgG to the cell surface.

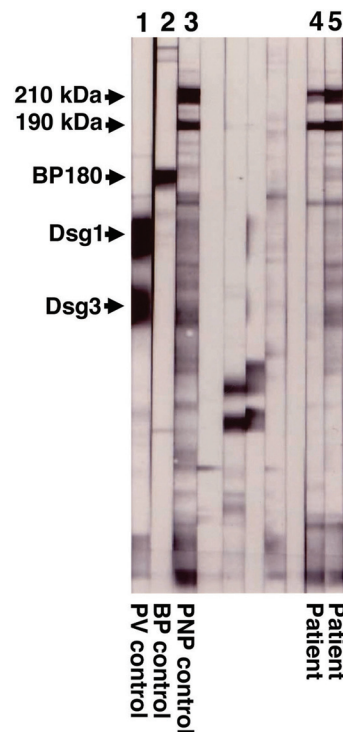


Fig. 2. Results of immunoblot analysis. Patient sera taken on two different occasions (lane 4 and 5) recognized 210-kDa envoplakin and 190-kDa periplakin, which were also detected by control paraneoplastic pemphigus (PNP) serum (lane 3). Lanes 1–3 show the reactivity of the control sera. Pemphigus vulgaris serum reacted with 160-kDa desmoglein (Dsg) 1 and 130-kDa Dsg 3 (lane 1), and bullous pemphigoid (BP) serum with 180-kDa BP antigen (lane 2).

In a malignancy survey, whole body computed tomography revealed a 7-cm mass within the abdominal cavity (Fig. 3a). Surgical resection was performed. A multi-nodular tumour, 10 × 7-cm in size, was located within the omentum and was removed en bloc. The tumour consisted of a uniform population of spindle cells with occasional mitoses (Fig. 3b). The spindle cells were arranged in short fascicles with nuclear palisading. The tumour was diagnosed as malignant GIST because the spindle cells stained positively for CD117 antigen. After the operation, the patient was treated with prednisolone at a dose of 60 mg per day. The mucosal lesions healed slowly with a remarkable improvement in the cutaneous lesions. The dose of prednisolone was slowly tapered. However, 4 months after the operation she died after the sudden development of dyspnoea.

DISCUSSION

In the majority of patients with PNP, the clinical course is progressive and often fatal, even if the underlying malignancies are removed completely. Respiratory failure, in particular, is a common terminal event. Approximately 30–40% of cases develop pulmonary injury by acantholysis of the bronchial epithelium (4). For diagnosis of PNP, detection of autoantibodies by immunoprecipitation is important. Compared with the immunoprecipitation, immunoblotting is easier and less hazardous. Although the immunoblotting detects 250-kDa/210-kDa desmoplakin I/II and 230-kDa bullous pemphigoid antigen less frequently, all the PNP sera exhibit characteristic reactivity with 210-kDa envoplakin and 190-kDa periplakin in immunoblotting with a human epidermal extract (3).

The majority of malignancies associated with PNP are lymphoproliferative disorders, including non-Hodgkin's B-cell lymphoma, chronic lymphocytic leukaemia, Castleman's disease and thymoma (1, 2). Other malignancies can also be associated with PNP, including soft tissue sarcomas (5–7), and even pancreas, uterine and hepatocellular carcinomas (8–10). To our knowledge, PNP has not yet been described in association with GIST. GIST is a rare primary neoplasm of the gastrointestinal tract, mesentery, or omentum. Although the exact pathogenesis is not fully known, it is thought to originate from the same

lineage as the interstitial cells of Cajal, pacemaker cells of the gastrointestinal tract. In many, but not all cases of GIST, mutations occur in KIT proto-oncogene, a tyrosine kinase receptor, which leads to ligand independent activation (11). The tumour size and mitotic count are prognostic factors. The present case was considered to involve an aggressive tumour because it was larger than 5 cm with more than five mitoses per 50 high-powered field (12, 13). This case suggests that GIST can be added to the list of associated tumours in PNP.

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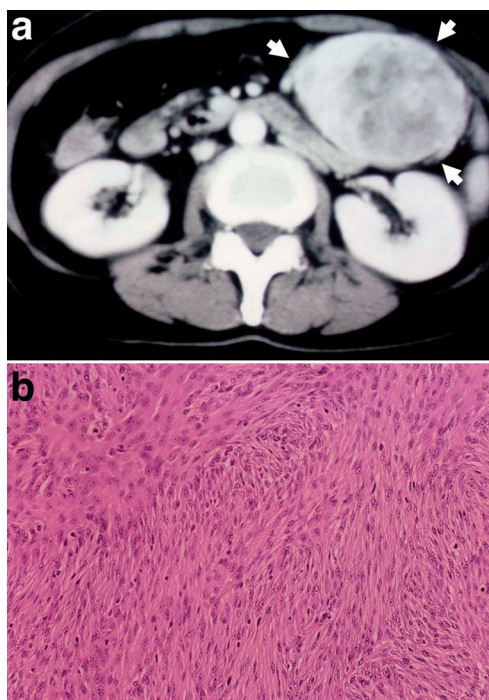


Fig. 3. Abdominal gastrointestinal stromal tumour. (a) Abdominal computed tomography showing the tumour mass (arrows). (b) Surgical resection biopsy. Spindle-shaped cells are arranged in cords and were associated with atypical mitoses (haematoxylin and eosin (H&E) $\times 200$).