

SHORT COMMUNICATION

A Typical Case of Paraneoplastic Pemphigus Without Detection of Malignancy: Effectiveness of Plasma Exchange

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Paraneoplastic pemphigus (PNP) is an autoimmune blistering disease, which presents Stevens-Johnson syndrome-like mucocutaneous lesions and graft-versus-host disease-like histopathological findings and is associated most commonly with lymphoproliferative neoplasms (1–3). Various plakin family proteins are the major autoantigens, by which the diagnosis of PNP can be made with a high sensitivity and specificity (4). However, PNP cases without detectable malignancy have also been reported (5–7). In addition, PNP is now known to show distinct features from classical pemphigus, including non-acantholytic histological changes (3), pathogenic role of cellular immunity (8) and involvement of extracutaneous organs (7, 9, 10). Particularly, PNP-related bronchiolitis obliterans (BO) is always lethal (7, 10).

We present a patient with clinically and immunologically typical PNP, who showed several unique findings and distinct efficacy of plasma exchange (PE) therapy.

CASE REPORT

A 67-year-old Japanese woman developed erythemas on the skin and painful oral mucosal lesions 2 months ago. Physical

examination revealed widespread violaceous erythemas with pityriatic scales on the trunk (Fig. 1a) and extensive ulcerative oral mucosal lesions (Fig. 1b). The conjunctivae were not affected. Mild dyspnea and hypoxaemia were also noticed.

A biopsy specimen from the lower lip showed extensive lichenoid interface dermatitis but no apparent acantholysis in the epithelium (Fig. 2a). Direct immunofluorescence revealed deposition of C3 (Fig. 2b) but not IgG, to keratinocyte cell surfaces in the lower epithelium. Indirect immunofluorescence of 1M NaCl-split skin sections demonstrated circulating IgG and IgA antibodies reactive with the epidermal side of the split (Fig. 2c, d). Indirect immunofluorescence of rat bladder and monkey oesophagus sections showed positive IgG reactivity (Fig. 2e, f).

Enzyme-linked immunosorbent assays (ELISAs) detected autoantibodies to Dsg3 (index 27.1, cut off <7), but not to either Dsg1 or BP180. Novel ELISAs of mammalian recombinant proteins of human desmocollins 1–3 (Dsc1–3) detected no IgG or IgA antibodies to any Dscs (Teye K, et al., manuscripts in preparation). Immunoblotting of normal human epidermal extracts showed strong IgG immunoreactivity with both the 210 kDa envoplakin and the 190 kDa periplakin (Fig. 2g). Immunoblotting also showed strong IgG, but not IgA, reactivity with recombinant protein of BP180 C-terminal domain (Fig. 2h), but not of BP180 NC16a domain.

From these clinical, histopathological and immunological results, diagnosis of PNP was made, although immunoreactivity suggesting anti-BP 180 type mucous membrane pemphigoid was also detected.

The patient was treated with steroid pulse therapy (1 g methylprednisolone, 3 days), followed by combination of oral prednisolone (1.0 mg/kg/day) and cyclosporine (2.8 mg/kg/day). High dose intravenous immunoglobulin (400 mg/kg/day, 5 days) was also used. However, because these therapies were ineffective, the patient underwent 4 rounds of PE. This therapy greatly improved the mucocutaneous lesions (Fig. 1c). Nevertheless, the respiratory condition, which we considered PNP-related BO, gradually worsened. She developed cough and dyspnea at both rest and exertion. Spirometry showed severe airway obstruction with forced expiratory volume of 0.42 l (38% predicted) in 1 s (FEV1). She was treated with bronchodilator and inhalational anticholinergic drug with oral prednisolone and cyclosporine, but pulmonary disorder was progressive, and the patient died of respiratory failure 9 months after the onset of the mucocutaneous lesions. One month before she died, the mucocutaneous lesions were still in remission, indicating that the effects continued after the last PE.

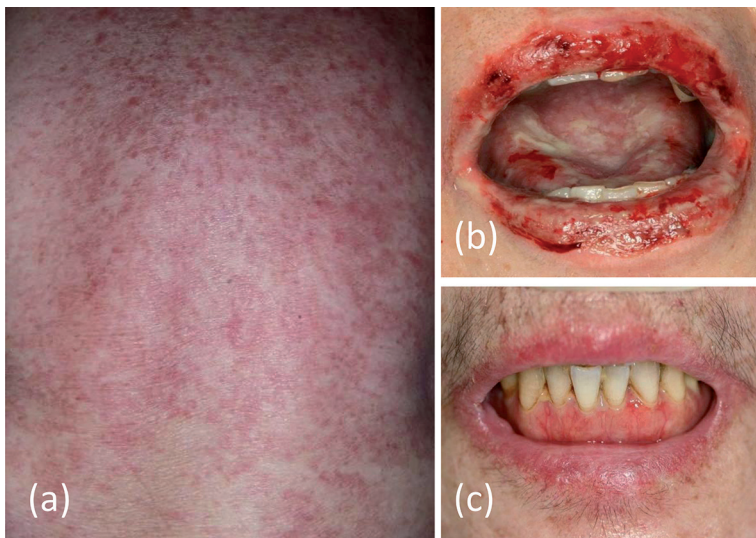


Fig 1. Clinical features on the trunk at the first visit (a). Mucosal lesions on the lips and tongue at the first visit (b). Clinical findings on the oral mucosa after the plasma exchange therapy (c).

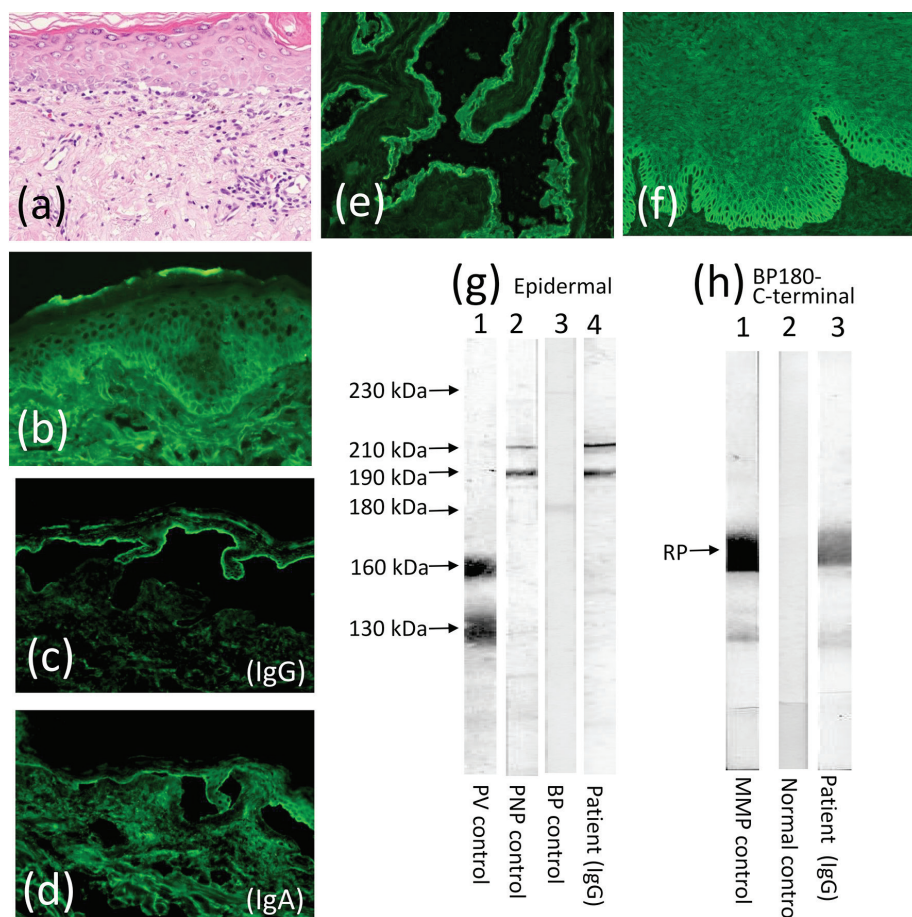


Fig. 2. Histopathological features (HE stain, $\times 200$) (a). Direct immunofluorescence for C3 deposition ($\times 200$) (b). Indirect immunofluorescence (IIF) of 1M NaCl-split skin sections for IgG and IgA antibodies ($\times 200$) (c, d). IIF of sections of rat bladder (e) and monkey esophagus (f) ($\times 200$) (e, f). Immunoblot analyses of normal human epidermal extracts (g) and recombinant protein of BP180 C-terminal domain (h) as substrates. The positions of 230 kDa BP230, 210 kDa envoplakin, 190 kDa periplakin, 180 kDa BP180, 160 kDa Dsg1, 130 kDa Dsg3 and recombinant protein (RP) are shown. PV: pemphigus vulgaris. BP: bullous pemphigoid.

DISCUSSION

One of the atypical points of our case was the failure to detect malignancy by careful investigation including various imaging studies. This is probably due to a too small size of a possible occult tumour in this case, which was also suggested in some previous reports (5–7). As an autopsy was not performed, the presence of malignancy was not confirmed. However, our patient showed typical clinical and laboratory findings for PNP. The absence of acantholysis in histopathology in our case is also a common feature in PNP (3), although acantholysis is a critical diagnostic criterion for classical pemphigus. Direct immunofluorescence detected cell surface deposition only of C3 but not of IgG. However, as bullous pemphigoid cases sometimes show deposition of C3 but not IgG, this absence of IgG staining may occur in PNP cases with severe damage of the epidermis (2). Ishii et al. (11) showed that ELISAs for Dsgs were more sensitive than immunoblotting. Therefore, it is reasonable that the anti-Dsg3 antibodies were positive in our case by ELISA, but not by immunoblotting.

Thus, some findings in our case, which may be inconsistent to the criteria of PNP, can be explained. In addition, other clinical and immunological features in this case were typical for PNP, including characteristic

oral mucosal ulcerative condition, lichenoid interface dermatitis changes in histopathology, positive immunofluorescence reactivity with rat bladder epithelium, strong immunoblot detection of antibodies to envoplakin and periplakin, positive IgG anti-Dsg3 antibodies, and the presence of PNP-related BO. Therefore, this case is safely diagnosed as PNP.

PNP is reported to develop not only by autoantibodies but also autoreactive T lymphocytes (8). We consider that T lymphocytes activated by cytokines might contribute to the histopathological lichenoid tissue reaction in our case. This assumption may explain the excellent efficacy of PE, which should remove cytokines more efficiently than plasmapheresis. In spite of the efficacy of PE on the mucocutaneous lesions, the respiratory symptom proved to be fatal, suggesting distinct pathomechanisms between mucocutaneous and respiratory conditions.

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