RESEARCH LETTER

Paraneoplastic Pemphigus Mimicking Pemphigus Herpetiformis – Overlap of Two Diseases

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To the Editor,

A 53-year-old woman was referred to our department due to blisters on both lower limbs. She had been diagnosed with diffuse large B-cell lymphoma and bronchiolitis obliterans 2 years earlier. A month before the initial visit to our department, the patient developed pneumothorax. Her medical history included uterine myoma, Hashimoto's disease, bilateral retinal detachment, bronchial asthma and hypertension. Physical examination revealed erythema annulare with blisters on both thighs and erosions on the soft palate, buccal mucosa and lips (**Fig. 1a**). The pemphigus disease area index was 9. A biopsy of the thigh revealed eosinophilic pustules and spongiosis without acantholysis in the epidermis. Eosinophils and lymphocytes infiltrated the perivascular region of the upper dermis (Fig. 1b). Blood tests revealed eosinophilia (1183/μL). Direct immunofluorescence showed deposits of the patient's IgG and C3 on the cell surface of the epidermis (Fig. 1c). The patient's IgG reacted with the transitional epithelium of the rat bladder and on the epidermal side of the 1M NaCl split skin in indirect immunofluorescence (Fig. 1d and e). The chemiluminescent enzyme immunoassay for desmoglein (Dsg) 3 was 928 U/mL, whereas those for Dsg1 and BP180 were negative. Enzyme-linked immunosorbent assay (ELISA) for BP230 was negative. ELISAs for desmocollin 1–3 established previously (1) were negative. Immunoblotting using human epidermal extracts revealed the patient's IgG reaction to a 210 kDa envoplakin, 190 kDa periplakin and 130 kDa Dsg3. Immunoblotting using BP180 NC16A recombinant protein was positive for the patient's IgG (Fig. 1f and g). Although the clinical and histological findings were consistent with pemphigus herpetiformis (PH), the final diagnosis of paraneoplastic pemphigus (PNP) was made according to the criteria proposed by the European Academy of Dermatology and Venereology (EADV) guidelines (2). Because the patient had a pneumothorax, the treatment was initiated with a low dose of prednisolone (10 mg/day) and diaminodiphenyl sulfone 50 mg/day. The skin and oral manifestations resolved in 3 weeks, and prednisolone was tapered.

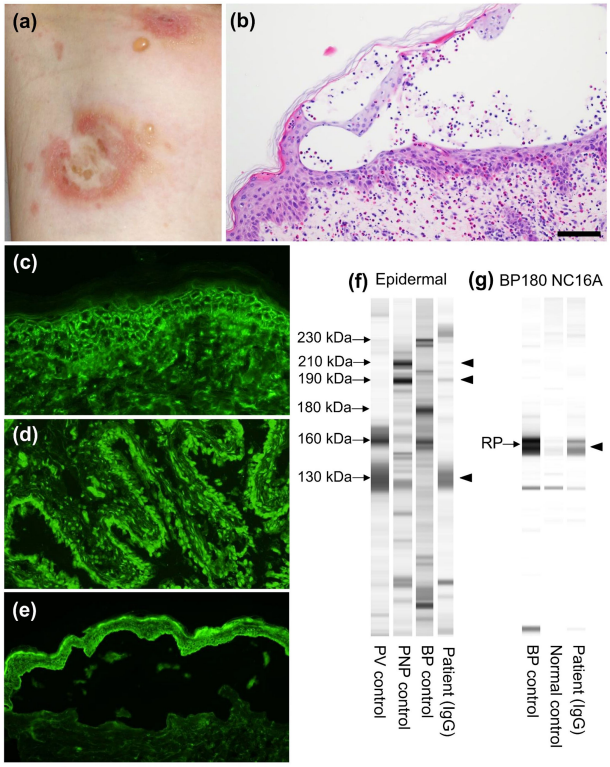

Fig. 1. Clinical, histological and immunological findings in this case. (A) Erythema annulare with blisters on the right thigh. (B) Eosinophilic pustulosis and eosinophil infiltration in the dermis (HE, x200) (scale bar: 100 μm). (C) Deposition of patient's IgG on the cell surface of keratinocytes in direct immunofluorescence. The patient's IgG reaction to the rat bladder epithelium (D) and the epidermal side of 1M split skin (E) in indirect immunofluorescence. Immunoblotting using epidermal extracts showing 210 kDa, 190 kDa and 130 kDa bands (F), and that using the recombinant protein (RP) of the BP180 NC16A domain showing the expected band as the RP (G) for the patient's IgG. Arrowheads indicate bands positive for the patient's IgG. Abbreviations: PV, pemphigus vulgaris; BP, bullous pemphigoid.

PH is a form of pemphigus reported by Jablonska et al. in 1975 and characterized by intraepidermal blistering and eosinophilic sea surface conditions with a clinical and histologic picture resembling dermatitis herpetiformis (3). To our knowledge, 10 cases of PH with neoplasms including haematologic tumours have been reported (4). Upon our detailed review of the 10 cases in the literature, immunological tests necessary for the diagnosis of PNP were not adequately performed in 8 of the 10 cases, leaving the possibility that these cases could present PNP. We summarized 3 case reports that were clinically considered PH but were reported as PNP and the present case (**Table I**). Cases 3 and 4 fulfilled the laboratory criteria of the EADV guidelines. Case 2 showed a 178 kDa band in immunoblotting, which is now considered an α2-macroglobulin-like 1 protein. Of note, case 3 was reported as "paraneoplastic pemphigus herpetiform". Although the EADV guidelines classify

Table I. Reported cases of paraneoplastic pemphigus exhibited clinical and histopathological features consistent with herpetiform pemphigus

Case	Neoplasm	Clinical findings	Histopathology	Immunofluorescence	ELISA	Immunoblotting	Reference
Case 1 48F	Ovarian cancer	Erythematous annular and targetoid papules/plaques on the trunk and extremities. No mucosal involvements.	Eosinophilic spongiosis with intercellular oedema, lymphocytic exocytosis, superficial perivascular infiltrate of lymphocytes and scattered eosinophils	DIF: IgG and C3 on the CS IIF: not reported	Dsg3 + Dsg1 – BP230 –	Not reported	Rubin et al.5
Case 2 68F	Lung cancer	Erythematous annular plaques with central crusts and scales on the trunk and extremities. No mucosal involvements.	Intraepidermal suprabasilar vesicles with eosinophilic infiltration in superficial dermis	DIF: IgG on the CS IIF: IgG on the CS of monkey esophagus epithelium	Dsg3 + Dsg1 – BP180 – BP230 – Dsc1 – Dsc2 – Dsc3 –	Dsg3 + 178–kDa unknown protein + Envoplakin – Periplakin –	Prado et al.6
Case 3 81F	Follicular B-cell non-Hodgkin lymphoma	Erythematous and desquamative plaques and confluent skin lesions on the chest and groin. Erosions on the vermilion of the lips and the tongue and in the oral cavity.	Eosinophilic and lymphocytic spongiosis	DIF: IgG and C3 on the CS IIF: IgG on the CS of normal human epidermis and transitional epithelium of murine bladder	Dsg3 + Dsg1 – Dsc1 – Dsc2 + Dsc3 +	Envoplakin + Periplakin +	Gallo et al.7
Case 4 53F	Diffuse large B-cell lymphoma	Annular erythema, erosions and blisters on the lower extremities, popliteal fossae along with erosions in the oral mucosa	Intraepidermal blisters containing eosinophils and eosinophilic spongiosis.	DIF: IgG and C3 on the CS IIF: IgG on transitional epithelium of the rat bladder	Dsg3 + Dsg1 – BP180 – Dsc1 – Dsc2 – Dsc3 –	Dsg3 + Envoplakin + Periplakin + BP180NC16A recombinant protein +	The present case

CS:cell surface; DIF:direct immunofluorescence; Dsc:desmocollin; Dsg:desmoglein; IIF:indirect immunefluorescence.

clinical manifestations into 5 major types: pemphigus-like, pemphigoid-like, lichen planus-like, erythema multiforme-like and graft vs host disease-like, we consider that a PH-like type of PNP also exists based on the above findings. Clinicians should consider that a PH-like phenotype can be observed in PNP. To avoid misdiagnosis, immunological tests for PNP are required when PH is diagnosed. Further studies are required to clarify the features of PH-like type PNP.

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Data availability statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

The authors have no conflicts of interest to declare.

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