SHORT COMMUNICATION

Transition from Paraneoplastic Pemphigus to Bullous Pemphigoid after a 26-month Remission

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Paraneoplastic pemphigus (PNP) is a rare, life-threatening autoimmune disorder associated with underlying malignancies (1). Although classified within the pemphigus, PNP is distinguished by multi-organ involvement, including skin blisters, erythema multiforme-like lesions, lichenoid dermatitis, severe panstomatitis, and bronchiolitis obliterans. These diverse manifestations are likely driven by autoantibodies targeting a broad range of autoantigens, including plakin family proteins (envoplakin, periplakin, desmoplakin I/II, BP230), desmogleins (Dsg1/3), desmocollins (Dsc1-3), and collagen XVII (COL17, BP180). While the precise pathology of PNP remains unclear, characterizing the detailed autoantigen profile and its temporal dynamics may provide important mechanistic insights.

Here, we report a PNP case responsive to initial treatment, which developed recurrent blistering 26 months after remission. At that time, autoantibody profiles were consistent with bullous pemphigoid (BP) rather than PNP, suggesting a transition from PNP to BP. This case highlights the differential persistence of autoantibodies targeting distinct antigens and indicates the importance of long-term autoantibody monitoring in PNP with overlapping autoantibody profiles.

CASE REPORT

An 84-year-old Asian male developed widespread skin eruptions on his trunk and extremities, unresponsive to topical betamethasone butyrate propionate. As the condition progressed to blisters and erosions extending to the face and oral mucosa, accompanied by systemic symptoms including fever, anorexia, and general fatigue, he was referred for further evaluation and treatment.

At the initial visit, the patient exhibited multiple erosions, crusts, blisters, and hemorrhagic blisters on his trunk, extremities, face, and scrotum (**Fig. 1**A, B). Mucosal involvement was observed in the oral cavity, vermilion border of the lips, and conjunctiva (Fig.

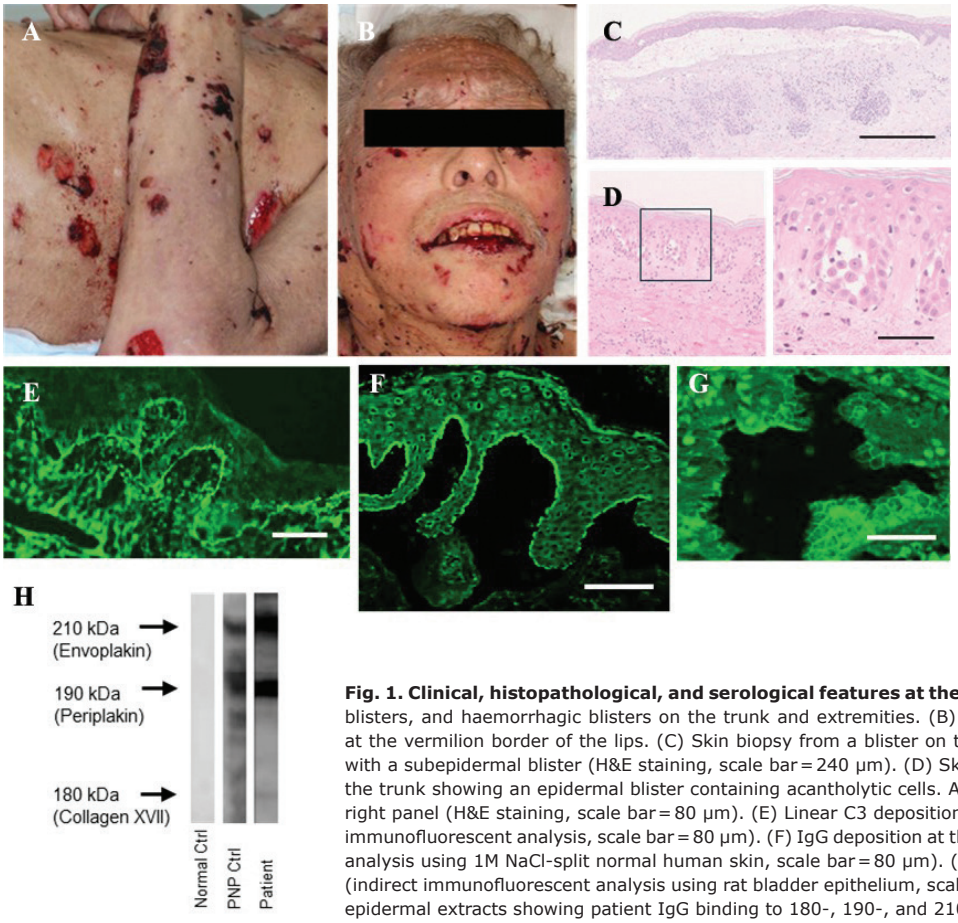

Fig. 1. Clinical, histopathological, and serological features at the initial visit. (A) Multiple erosions, crusts, blisters, and haemorrhagic blisters on the trunk and extremities. (B) Facial erosions and mucosal involvement at the vermilion border of the lips. (C) Skin biopsy from a blister on the lower leg showing interface dermatitis with a subepidermal blister (H&E staining, scale bar = 240 μm). (D) Skin biopsy from an erythematous lesion on the trunk showing an epidermal blister containing acantholytic cells. A higher-magnification image shown in the right panel (H&E staining, scale bar = 80 μm). (E) Linear C3 deposition at the dermal–epidermal junction (direct immunofluorescent analysis, scale bar = 80 μm). (F) IgG deposition at the blister roof (indirect immunofluorescent analysis using 1M NaCl-split normal human skin, scale bar = 80 μm). (G) IgG deposition at the cell–cell contacts (indirect immunofluorescent analysis using rat bladder epithelium, scale bar = 50 μm). (H) Immunoblotting using epidermal extracts showing patient IgG binding to 180-, 190-, and 210-kDa proteins.

Table I. Peripheral autoantibody titres at the initial visit and 28 months later

Autoantibodies	0 month	28 months	Normal range (U/mL)
	ELISA index (U/mL)		
Anti-collagen XVII NC16a IgG (CLEIA)	**37.6**	**51.1**	< 10
Anti-BP230 IgG	**16.4**	**81.5**	< 10
Anti-Dsg1 IgG	4.3	1.7	< 20
Anti-Dsg3 IgG	4.3	2	< 20
Anti-Dsc1 IgG	**0.334**	0.118	< 0.304
Anti-Dsc2 IgG	**2.111**	0.076	< 0.161
Anti-Dsc3 IgG	0.106	0.104	< 0.173
	IB		
Anti-envoplakin IgG	+	-	
Anti-periplakin IgG	+	-	
Anti-collagen XVII IgG	+	+	

ELISA: enzyme-linked immuno-sorbent assay; CLEIA: chemiluminescent enzyme immunoassay; IB: immunoblotting; Dsg: desmoglein; Dsc: desmocollin. Values in bold indicate levels above the normal range.

1B). Histopathological examination of a skin biopsy indicated acantholysis, epidermal and subepidermal blistering, and interface dermatitis (Fig. 1C, D). Direct immunofluorescence (DIF) analysis showed linear C3 deposition at the dermal–epidermal junction (DEJ) (Fig. 1E). Indirect immunofluorescence (IIF) using normal human skin revealed linear IgG, but not IgA, deposition at the DEJ. IIF with 1M NaCl-split skin showed IgG deposition at the blister roof (Fig. 1F). IIF on rat bladder epithelium revealed IgG deposition at cell–cell junctions (Fig. 1G). Serological analysis by chemiluminescent enzyme immunoassay (CLEIA) or enzyme-linked immunosorbent assay (ELISA) detected autoantibodies against COL17 NC16a (37.6 U/mL; normal: < 10 U/mL), BP230 (16.4 U/mL; normal: < 10 U/mL), Dsc1 (0.334 U/mL; normal: < 0.304 U/mL), and Dsc2 (2.111 U/mL; normal: < 0.161 U/mL), while IgG against Dsg1, Dsg3, or Dsc3 was undetectable (**Table I**). Immunoblotting using epidermal extracts detected IgG bindings to 180, 190, and 210 kDa proteins corresponding to COL17, periplakin, and envoplakin, respectively (Fig. 1H, Table I). A mucosal biopsy was not performed. A pulmonary function test and chest computed tomography scan ruled out bronchiolitis obliterans. Fluorodeoxyglucose positron emission tomography (FDG-PET) scan revealed increased uptake in the oesophagus, suggesting oesophageal cancer. No other gastroenterological or haematological disorders were identified through these investigations or blood tests. Based on the clinical and laboratory findings, the patient was diagnosed with PNP. The pemphigus disease area index (PDAI) score at the initial visit was 65.

Treatment was initiated with intravenous methylprednisolone pulse therapy (500 mg/day), followed by oral prednisolone (PSL) at 60 mg/day (1.0 mg/kg/day). Initially, PNP was not diagnosed, and a drug eruption was considered, leading to rapid PSL tapering. However, the skin lesion worsened. At week 3 with PSL reduced to 30 mg/day, the PDAI score increased to 89. After confirming the PNP diagnosis, intravenous immunoglobulin therapy was administered, and PSL was increased back to 60 mg/day, leading to gradual improvement. By week 8, the PDAI score had decreased to 0 with PSL at 30 mg/day. Thereafter, anti-COL17 IgG levels declined to < 3.0 U/mL, and no recurrence of skin eruption was observed for 26 months. After clinical remission, oesophageal endoscopy evaluated a lesion suggested by PET-CT. This revealed a 2 cm Barrett's adenocarcinoma without metastasis (stage T1aN0M0). Although surgical resection was considered, the cancer was managed conservatively due to the patient's advanced age, poor performance status, and stable PNP control with minimal immunosuppressive treatment.

When PSL was tapered to 2 mg/day at 28 months, the patient developed a few tense and haemorrhagic blisters on his palms and fingers, without mucosal involvement (**Fig. 2**A). A skin biopsy from a palmar blister revealed subepidermal blistering with neutrophilic and eosinophilic infiltration, without acantholysis or interface dermatitis (Fig. 2B). DIF showed linear C3 deposition at the DEJ, consistent with the previous finding (Fig. 2C). IIF using 1M NaCl-split skin demonstrated linear IgG deposition at the blister roof (Fig. 2D), whereas IIF on rat bladder epithelium did not show IgG deposition (Fig. 2E). Serological analysis detected autoantibodies against COL17 NC16a (51.1 U/mL) and BP230 (81.5 U/mL), while IgG against Dsc1 or Dsc2 was undetectable this time (see Table I). Immunoblotting no longer detected IgG against 190 kDa or 210 kDa proteins, which was previously observed (Fig. 2F, Table I). Based on the clinical and laboratory findings, the patient was diagnosed with BP this time. The bullous pemphigoid disease area index (BPDAI) score was 10. After increasing PSL to 7 mg/day with topical clobetasol, the BPDAI decreased to 0, and anti-COL17 IgG levels again dropped to < 3.0 U/mL.

DISCUSSION

In the present case, the patient's clinical features and autoantibody profile transitioned from PNP to BP following the 26-month remission. We suggest that this is unlikely to be a coincidental BP onset after the PNP

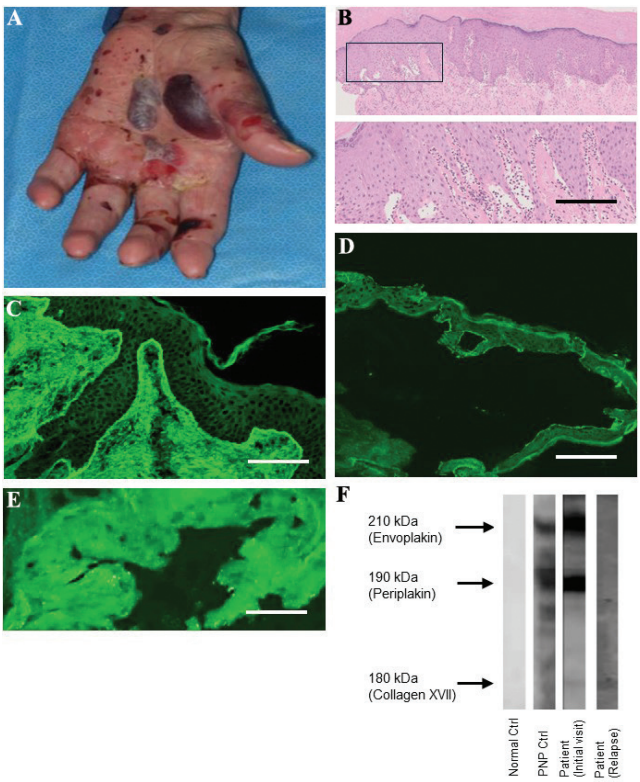

Fig. 2. Clinical, histopathological, and serological features at 28 months from the initial visit. (A) Multiple blisters and haemorrhagic blisters on the palm and fingers. (B) Skin biopsy from the palmar blister showing subepidermal blister with neutrophilic and eosinophilic infiltration (H&E staining, scale bar = 100 µm). (C) Linear C3 deposition at the dermal–epidermal junction (direct immunofluorescence staining, scale bar = 80 µm). (D) IgG deposition at the blister roof (indirect immunofluorescent analysis using 1M NaCl-split normal human skin, scale bar = 150 µm). (E) No IgG deposition (indirect immunofluorescent analysis using rat bladder epithelium, scale bar = 60 µm). (F) Immunoblotting using epidermal extracts showing IgG binding to 180-kDa protein.

remission, based on the rarity of both diseases; however, coincidental occurrence cannot be entirely ruled out. While PNP and BP are both categorized as autoimmune blistering diseases, they exhibit distinct immunological and clinical characteristics. BP is characterized by autoantibodies against COL17 and BP230, which directly contribute to blister formation (2). In contrast, PNP presents a broader autoantigen profile, including desmosomal proteins and plakin proteins, leading to multi-organ involvement (1). Although PNP is classified as a "pemphigus", approximately 40% of PNP cases exhibit autoantibodies against COL17 (3), indicating that the autoantibody profile in PNP often overlaps with that of BP. This overlap likely contributed to the subepidermal blisters sometimes observed in PNP, including the present case.

A novel aspect of this case is the selective persistence of anti-COL17 autoantibodies following PNP remission, whereas autoantibodies against desmocollins and plakin family proteins were no longer detectable (see Table I). Studies on vaccine-induced antibody responses indicate that antibody durability is influenced by factors such as inflammatory milieu and antigen-specific properties (4). As COL17, desmocollins, and plakin family proteins are all expressed in the skin, differences in the inflammatory milieu during antigen presentation are unlikely to contribute to the persistence of humoral immunity against COL17 in this case. Instead, antigen-specific immune responses, possibly influenced by the structural properties and/or relative abundance, may contribute to its prolonged humoral immunity against COL17. Notably, Barrett's adenocarcinoma expresses COL17 (5), suggesting cancer immunity may have contributed to sustained autoantibody production against COL17. Additionally, systemic corticosteroids can promote a shift from type 1 to type 2 inflammation (6), which may have influenced the immunological transition from PNP, characterized by both humoral and cellular immune responses, to BP, a disease driven by type 2 humoral immunity.

Clinically, our findings suggest that PNP patients with anti-COL17 antibodies may remain at risk of BP even after clinical remission of PNP. Long-term autoantibody monitoring is crucial for early detection of disease transitions, enabling timely intervention and optimal management. Regular follow-up and serological testing may help tailor treatment strategies and prevent severe disease progression.

The authors have no conflicts of interest to declare.

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