

## Sequential Occurrence of Pemphigus Vulgaris and Palmoplantar Pustulosis: Possible Role of Cytokine Profile

Akihiko Asahina<sup>1</sup>, Kazuko Uno<sup>2</sup> and Hideki Fujita<sup>1</sup>

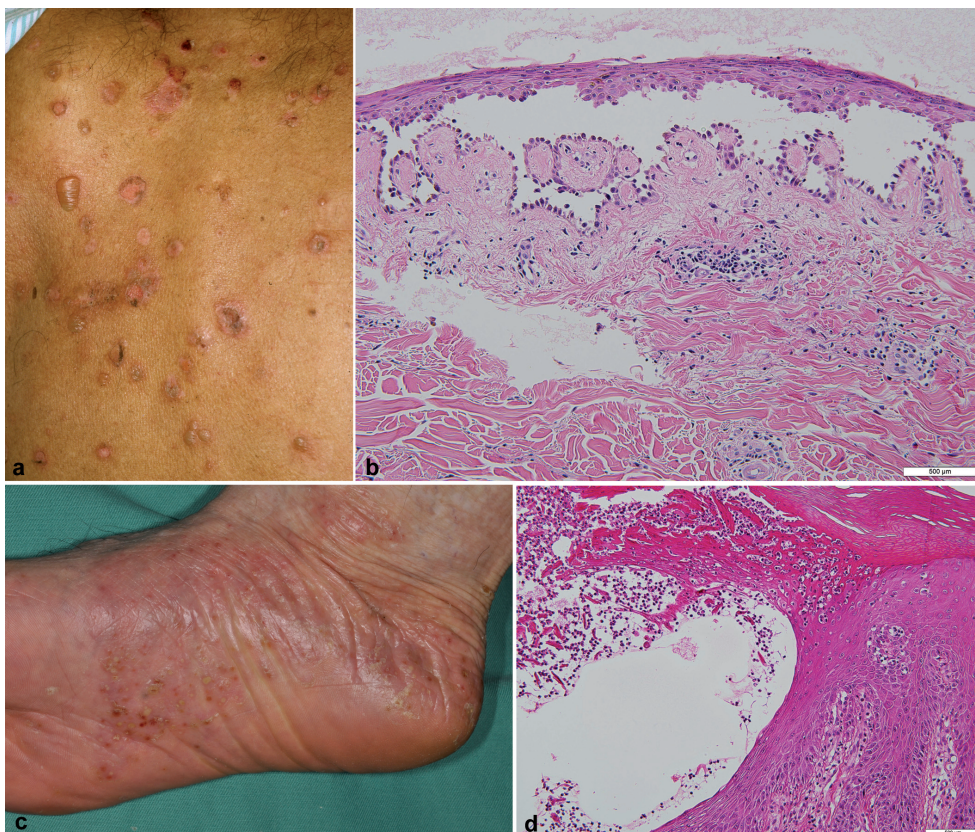
<sup>1</sup>Department of Dermatology, National Hospital Organization, Sagami National Hospital, 18-1 Sakuradai, Minami-ku, Sagami-hara Kanagawa 252-0392, and <sup>2</sup>Louis Pasteur Center for Medical Research, Kyoto, Japan. E-mail: asahina-ky@umin.ac.jp  
Accepted March 3, 2011.

Some autoimmune bullous diseases are known to develop in patients with psoriasis. While associations of psoriasis with bullous pemphigoid (BP) and anti-laminin gamma-1 pemphigoid are relatively common (1), pemphigus foliaceus and pemphigus herpetiformis are less frequently associated with psoriasis. In particular, there are only a limited number of reports on pemphigus vulgaris (PV) (2–5). Palmoplantar pustulosis (PPP) is a peculiar and localized form of pustular psoriasis, although its classification is debatable (6). We report here a patient in whom PV and PPP developed sequentially; measurements of multiple cytokines and chemokines in the serum suggested the possible involvement of tumour necrosis factor (TNF)- $\alpha$  in the clinical course.

### CASE REPORT

A 71-year-old man was referred to our hospital with bullae and erosions of one-month duration. He had been diagnosed with PPP 15 years previously, but it had resolved completely in 5 years by topical glucocorticoid application, and he received no further

treatment for PPP. On physical examination, multiple flaccid bullae and erosions were located on the trunk and extremities with occasional erythema (Fig. 1a). Nikolsky sign was noted. He also had a painful erosion in the oral cavity. A biopsy specimen taken from the back showed suprabasal acantholysis and mixed inflammatory cell infiltration composed of lymphocytes, plasma cells, and eosinophils (Fig. 1b). Direct immunofluorescent staining showed immunoglobulin G and C3 deposits in the intercellular spaces. The patient's serum was positive for both desmoglein 1 (index: 99; cut-off value: 14) and desmoglein 3 (index: 141; cut-off value: 7), confirming the diagnosis of PV. He received treatment with oral prednisolone, which was started at a dose of 50 mg/day and tapered gradually. The skin lesions resolved in 6 weeks. At 13 months with prednisolone at 5 mg/day, he noticed pustules with keratotic scaling on the palms and soles (Fig. 1c). A biopsy specimen from a pustule of the left foot showed spongiform subcorneal abscess formation, consistent with the recurrence of PPP (Fig. 1d). Serum anti-desmoglein 3 antibody was negative at that time. He had neither arthralgia nor eruptions in other areas. He was a moderate smoker, but he had not changed his smoking habits over time. He had had no apparent focal infection that might have triggered PPP. Currently, his PPP lesions have persisted for another 2 years without PV, despite topical glucocorticoid application.



*Fig. 1.* (a) Multiple flaccid bullae, erosions, and erythema on the back. (b) Biopsy specimen from the back showing suprabasal acantholysis and mixed inflammatory cell infiltration. (Haematoxylin and eosin (H&E), original magnification  $\times 200$ . Scale bar: 500  $\mu\text{m}$ ). (c) Pustules and erythematous keratotic scaling on the sole. (d) Biopsy specimen from a pustule of the sole showing spongiform subcorneal abscess formation. (H&E, original magnification  $\times 200$ . Scale bar: 500  $\mu\text{m}$ .)

We measured serum levels of cytokines and chemokines (Bio-Plex Pro™ Assays, Bio-Rad Laboratories, Hercules, CA, USA) and compared their profiles at three time-points, that is, before, one month after, and 2 years after the initiation of PV treatment. Blister fluid of PV before treatment was also analyzed (Table S1, available from: <http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1159>). Some chemokines were detected in the blister fluid at a much higher level than in the serum. Interleukin (IL)-5, IL-6, and IL-13 were also elevated in the blister fluid. Importantly, the serum IL-4 level did not decline, and the interferon (IFN)- $\gamma$  level did not increase after PV treatment. In contrast, the serum TNF- $\alpha$  level was the highest before PV treatment, and its level was also high in the blister fluid. Its serum level declined soon after treatment, and remained low after the PPP lesions emerged.

## DISCUSSION

Psoriasis is a well-known immune-mediated disorder where autoimmune processes may play a role. Alternatively, ultraviolet therapy, topical medications, and/or the inflammatory processes that occur in psoriatic skin may induce bullous diseases by damaging the dermo-epidermal junction or by evoking the production of autoantibodies (1). Some drugs are believed to behave as a triggering agent for this process (4). Our patient is unique, in that he was affected by PPP and PV. Compared with psoriasis, PPP is occasionally associated with other autoimmune diseases, including thyroid autoimmunity, with an incidence of 16–25%, and also vitiligo, alopecia, Sjögren's syndrome, and rheumatoid arthritis (6). On conducting a search of the English literature, however, we were unable to find patients with PPP associated with any kind of bullous diseases.

An interesting feature in our patient was that PPP and PV occurred sequentially and did not coexist. The Th1-Th2 balance may explain this alternative appearance. Yasukawa et al. (7) reported a case of generalized pustular psoriasis that appeared during glucocorticoid therapy for BP. Serum cytokine levels and the results of an immunohistochemical study suggested a shift from Th2- to Th1-dominance. Sugita et al. (8) also showed Th2 cell fluctuation in association with the reciprocal occurrence of BP and psoriasis. In our patient, the serum IL-4 level did not decline after PV treatment, and IFN- $\gamma$  was detected even before PV treatment. This is consistent with the idea that, in contrast to BP, PV shows a mixed Th1/Th2 cytokine expression (9). Alteration of the Th1-Th2 balance alone does not appear to be an underlying mechanism of the clinical course in our patient.

Of note, the serum TNF- $\alpha$  level in our patient was elevated before PV treatment, declined significantly

after treatment, and remained low thereafter. Indeed, elevation of serum TNF- $\alpha$  (9), as well as *in situ* TNF- $\alpha$  mRNA expression (10), has been reported in PV patients. TNF- $\alpha$  may be involved in enhancing acantholysis (10), and anecdotal reports show that PV patients benefit from treatment with TNF antagonists. Furthermore, it is known that TNF- $\alpha$  antagonists may induce PPP-like eruption as a paradoxical cutaneous adverse effect in patients with rheumatic conditions (11). It is intriguing to speculate that the downregulation of TNF- $\alpha$  by treatment resulted in the amelioration of PV, but simultaneously triggered the occurrence of PPP in this autoimmune-prone individual.

## REFERENCES

1. Lazarczyk M, Wozniak K, Ishii N, Gorkiewicz-Petkov A, Hashimoto T, Schwarz R, et al. Coexistence of psoriasis and pemphigoid – only a coincidence? *Int J Mol Med* 2006; 18: 619–623.
2. Grunwald MH, David M, Feuerman EJ. Coexistence of psoriasis vulgaris and bullous diseases. *J Am Acad Dermatol* 1985; 13: 224–228.
3. Aytekin S, Inalöz HS, Harman M, Akdeniz S, Deveci E, Inalöz SS. Coexistence of psoriasis vulgaris and bullous disorders. *J Eur Acad Dermatol Venereol* 1999; 12: 185–187.
4. Daulat S, Detweiler JG, Pandya AG. Development of pemphigus vulgaris in a patient with psoriasis treated with etanercept. *J Eur Acad Dermatol Venereol* 2009; 23: 483–484.
5. Caldarola G, Carbone A, De Simone C, Pellicano R. Development of pemphigus vulgaris in a patient with psoriasis treated with cyclosporine. *J Am Acad Dermatol* 2010; 63: 356–357.
6. Yamamoto T. Extra-palmoplantar lesions associated with palmoplantar pustulosis. *J Eur Acad Dermatol Venereol* 2009; 23: 1227–1232.
7. Yasukawa S, Dainichi T, Kokuba H, Moroi Y, Urabe K, Hashimoto T, et al. Bullous pemphigoid followed by pustular psoriasis showing Th1, Th2, Treg and Th17 immunological changes. *Eur J Dermatol* 2009; 19: 69–71.
8. Sugita K, Kabashima K, Nishio D, Hashimoto T, Tokura Y. Th2 cell fluctuation in association with reciprocal occurrence of bullous pemphigoid and psoriasis vulgaris. *J Eur Acad Dermatol Venereol* 2007; 21: 569–570.
9. Baroni A, Perfetto B, Ruocco E, Greco R, Criscuolo D, Ruocco V. Cytokine pattern in blister fluid and sera of patients with pemphigus. *Dermatology* 2002; 205: 116–121.
10. Feliciani C, Toto P, Amerio P, Pour SM, Coscione G, Shivji G, et al. In vitro and in vivo expression of interleukin-1 $\alpha$  and tumor necrosis factor- $\alpha$  mRNA in pemphigus vulgaris: interleukin-1 $\alpha$  and tumor necrosis factor- $\alpha$  are involved in acantholysis. *J Invest Dermatol* 2000; 114: 71–77.
11. de Gannes GC, Ghoreishi M, Pope J, Russell A, Bell D, Adams S, et al. Psoriasis and pustular dermatitis triggered by TNF- $\alpha$  inhibitors in patients with rheumatologic conditions. *Arch Dermatol* 2007; 143: 223–231.