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Bullous Pemphigoid with Prominent Milium Formation

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SUMMARY Milia are very common superficial keratinous cysts, clinically seen as pearly white dome-shaped lesions with a diameter of 1-2 mm. Bullous pemphigoid (BP) is an autoimmune bullous disease characterized clinically by tense bullae on the extremities and trunk. The major target autoantigens of BP are BP180 and BP230. We report a 55-year-old Polish BP patient presenting prominent milium formation. Physical examination revealed multiple tense bullae on the erythemas scattered on the extremities and trunk. Histopathology revealed subepidermal blisters with infiltration of eosinophils in and around the blister. Direct immunofluorescence showed IgG and C3 depositions at basement membrane zone. Although indirect immunofluorescence of normal human skin sections was negative, indirect immunofluorescence of salt-split skin sections showed IgG reactivity with epidermal side. Immunoblotting showed that IgG antibodies in the serum reacted with recombinant protein of the BP180 NC16a domain. ELISA of BP180, but not BP230 and type VII collagen, showed positive results. Several months after oral prednisolone therapy, multiple large milia appeared on the healed BP lesions. Histopathology showed cysts with flaky keratinous inclusions in the mid-dermis. We diagnosed the patient as BP with milia. Since milia are occasionally found in BP, they are not a definite differential criterion from epidermolysis bullosa acquisita.

KEY WORDS: BP180, BP230, bullous pemphigoid, epidermolysis bullosa acquisita, milia

INTRODUCTION

Bullous pemphigoid (BP) is an autoimmune blistering disease affecting the elderly. BP is characterized clinically by tense bullae on the extremities and trunk, histopathologically by subepidermal blisters with eosinophilic infiltration, and immunologically by autoantibodies to BP180 and BP230 (1). Direct immunofluorescence of perilesional skin showed depositions of IgG and C3 at basement membrane zone (BMZ). Indirect immunofluorescence of normal human skin sections as a substrate detects circulating IgG anti-BMZ antibodies, which react with epidermal side of 1M NaCl-split skin sections (1).

Immunoblotting of normal human epidermal extracts as a substrate detects IgG antibodies reactive with BP180 and/or BP230 (1). Immunoblotting shows IgG reactivity with recombinant protein of the NC16a domain of BP180. In some BP patients, immunoblotting

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of concentrated culture supernatant of HaCaT cells shows reactivity with LAD-1, a well known autoantigen in linear IgA bullous dermatosis. IgG antibodies in patient sera show positive results in ELISAs of BP180 and BP230 (1). The diagnosis of BP is now made by combination of these methods.

BP rarely shows prominent milium formation, which is a hallmark of epidermolysis bullosa acquisita. We report a BP case with multiple large milia on the healed BP lesions, the diagnosis of which was confirmed by various immunological techniques.

CASE REPORT

A 55-year-old Polish female visited the Polish Institute of Skin Disease in September 2010, complaining of a 6-month history of generalized pruritic skin lesions. The diagnosis of autosensitization dermatitis due to intertriginous candidiasis was tentatively made, and the patient was treated with a combination of oral fluconazole 200 mg daily and topical clotrimazole/hydrocortisone, which was partially effective. However, one month later, blistering lesions appeared suddenly.

Physical examination revealed multiple tense bullae and crusts on erythemas scattered on the trunk and extremities (Fig. 1a). A biopsy was taken from the edge of the blister on the forearm with a scalpel. Histopathologically, a subepidermal blister with infiltration of eosinophils in and around the blister was found. Although indirect immunofluorescence of normal human skin sections was negative (Fig. 1b), indirect immunofluorescence of 1M NaCl-split skin sections showed that IgG antibodies in the patient serum reacted with the epidermal side of the split (Fig. 1c).

Immunoblotting of normal epidermal extracts showed that the patient serum reacted with neither BP230 nor BP180 (Fig. 1d). Immunoblotting showed IgG reactivity with recombinant protein of the NC16a domain of BP180, while immunoblotting of recombinant protein of C-terminus of BP180, purified human laminin-332, concentrated HaCaT cell culture supernatants and normal human dermal extracts showed negative results (Fig. 1d). Index value of enzyme-linked immunosorbent assay (ELISA) for BP180 was 50.0 (positive: cut-off >15), that for BP230 was 1.17 (negative: cut-off >9) and that for type VII collagen was 2.04 (negative: cut-off >6.14).

Although direct immunofluorescence could not be performed, we diagnosed this patient as having BP and started treatment with oral prednisolone 50 mg daily and ranitidine 300 mg daily, combined with a very strong topical corticosteroid. This treatment could control the lesion perfectly. One month later, the dose of prednisolone was reduced by 2.5 mg every 2 weeks. However, strong pruritus and superficial serous discharge occurred suddenly. Under suspicion of secondary bacterial infection, we started 3 cycles of 10-day regimen of fexofenadine 180 mg daily and doxycycline 100 mg daily, which cured the skin lesions.

Seven months later, multiple large milium-like lesions appeared on almost all the healed BP lesions, particularly on the wrists (Figs. 1e,f). A biopsy obtained from the lesion showed the normal appearing overlying epidermis and BMZ, and multiple cysts with squamous epithelial cell wall and flake-like keratinous inclusions in the mid-dermis, confirming the diagnosis of milia (Fig. 1g).

DISCUSSION

Milia are very common benign keratinous cysts of the skin, clinically seen as pearly white dome-shaped lesions, 1-2 mm in diameter (2). Primary and secondary milia are known (3). Secondary milia are associated with many dermatologic disorders, including epidermolysis bullosa hereditaria, epidermolysis bullosa acquisita, bullous lichen planus, porphyria cutanea tarda, burns, skin trauma, contact dermatitis, tattoo, cutaneous leishmaniasis, and iatrogenic application of nitrogen mustard or topical corticosteroids (3-5).

Concerning the association of milia with BP, there are conflicting systematic studies in addition to several case reports (3,6-10). Prost *et al*. report that 9 (52.9%) of 17 mucous membrane pemphigoid or epidermolysis bullosa acquisita patients, but none of 15 BP patients showed milium formation (7). In contrast, Venning *et al*. report that all 3 epidermolysis bullosa acquisita patients, one (11.1%) of 9 mucous membrane pemphigoid patients, and 7 (38.9%) of 18 BP patients showed an association with milia (8). Furthermore, using indirect immunofluorescence and immunoblotting, Venning *et al*. categorized BP into BP230 single positive BP (group 1), BP180 single positive BP (group 2) and indirect immunofluorescence positive and immunoblotting negative BP (group 3), and revealed that two (22%) of nine group 1 patients, one (17%) of six group 2 patients, and three (20%) of fifteen group 3 patients showed an association with milia (9). Finally, the largest study by Banfield *et al*. revealed an association of milia in 23 (31.1%) of 74 BP patients, who showed significantly higher association with HLA-DQ6 (10). However, the number and size of milia in the previous BP cases are much less, if compared with the prominent milium formation seen in our patients.

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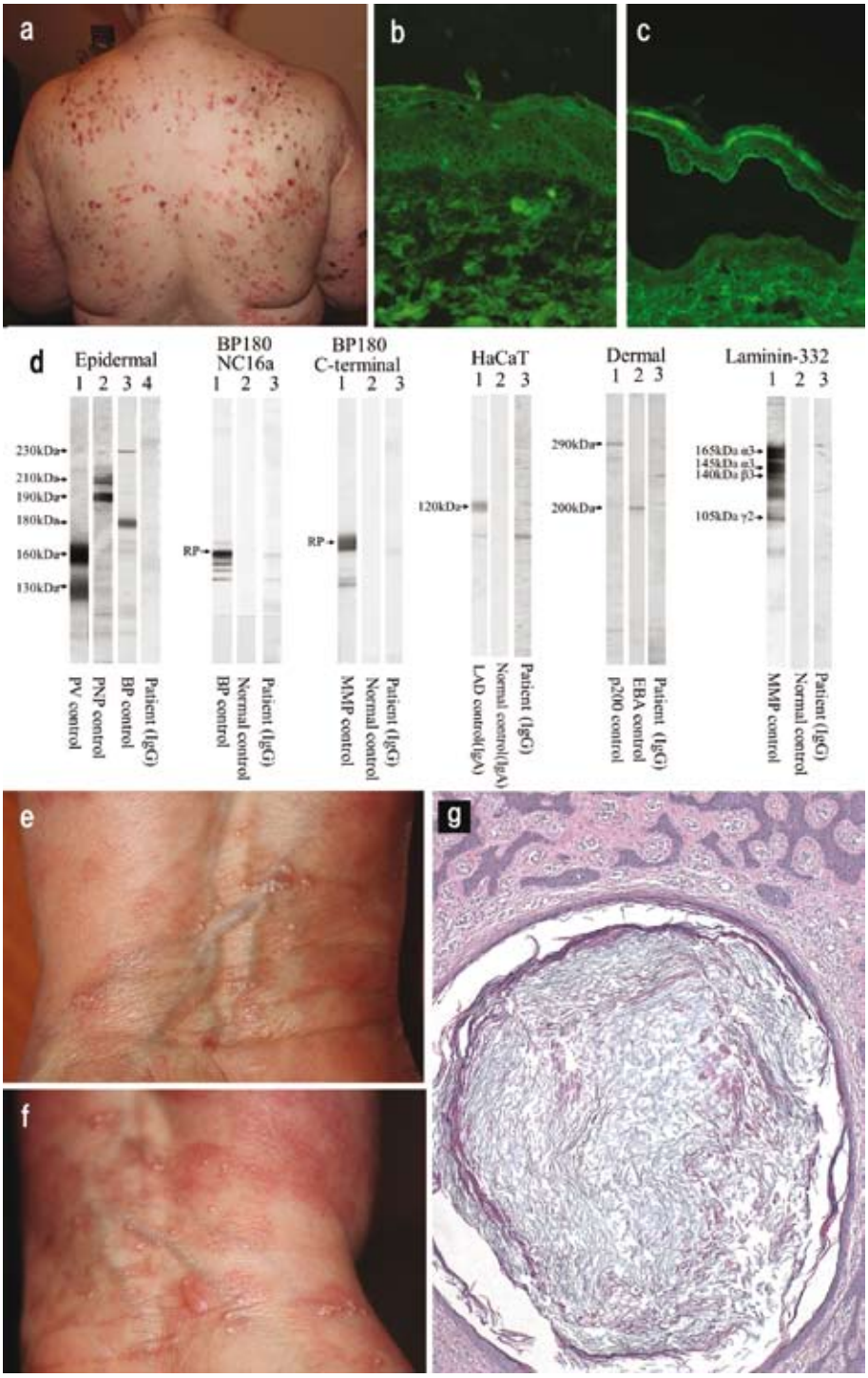

Figure 1. (a) Clinical feature on the upper back at the initial appearance; (b) indirect immunofluorescence of normal human skin section. No reaction to BMZ with weak cytoplasmic staining in the basal cells; (c) indirect immunofluorescence of 1M NaCl-split skin section; (d) immunoblotting of epidermal extract, recombinant proteins of BP180 NC16a and C-terminal domains, HaCaT cell culture supernatant, normal human dermal extract and purified human laminin-332; (e,f) clinical features of both wrists showing multiple milia; (g) histopathologic feature showing a milium (HE, X200).

Milia secondary to blisters or traumas are speculated to be produced through the regeneration process of disrupted sweat glands or hair follicles (3). Therefore, post-bullous milia should be temporary, and wait-and-see policy has been proposed (3). As milium formation is not very rare in BP, this is not a definite differential criterion from epidermolysis bullosa acquisita. Therefore, various immunologic diagnostic studies should be performed in cases of bullous skin disease with milium formation.

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