Two Cases of Generalized Pustular Psoriasis Followed by Acquired Bullous Disease

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We herein present two cases of generalized pustular psoriasis(GPP) followed by acquired bullous diseases during antipsoriatic management. Although there were several reports describing the coexistence of psoriasis vulgaris and autoimmune bullous diseases such as bullous pemphigoid or pemphigus vulgaris(PV), a coexistence of GPP and bullous disease was sparcely reported. In one patient, we could define atypical autoantigen which was distinct from the other known antigens in documented cases of bullous diseases. The other case was compatible with PV. The psoriatic lesions and bullous eruptions of the two patients cleared in several weeks after administration of cyclosporine. (Ann Dermatol 11(1) 41~46, 1999).

Key Words : Generalized pustular psoriasis, Acquired bullous disease.

The association of bullous disease such as bullous pemphigoid(BP) and psoriasis has often been reported[1-3]. However, it is not clear whether the occurrence of psoriasis with acquired bullous dermatoses represents a true correlative relationship[4]. Moreover, despite the frequent coexistence of these two skin diseases, the diagnosis of bullous diseases accompanied by psoriasis had been merely made on the basis of clinical features, histopathological findings, and routine direct immunofluoresecnce(DIF)[5-7]. To date, in the few reported cases, further investigations such as indirect immunofluorescence(IIF) studies on salt-split skin or immunoblotting or immunogenetic analysis have been carried out in order to elucidate the relationship of the two diseases[3,4,8]. Here, we report two cases representing the coexistence of psoriasis with acquired bullous dermatosis.

Received March 10, 1998
Accepted for publication June 5, 1998.
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CASE REPORTS

Case 1

A 63-year-old man without a preceding history of psoriasis was admitted when he developed generalized scaling erythemas and pustules covering more than 30% of his body surface(Fig. 1). His family history was insignificant. A negative porphyrin screen, FANA, LE-cell, anti- SSA(Ro)/SSB(La), anti-Sm, and anti-dsDNA were obtained. A skin biopsy from a pustule on his chest demonstrated intraepidermal Kogoj's spongiform pustules mainly filled with neutrophils and nuclear dusts, Munro's microabscess, hyperkeratosis, parakeratosis, prominent elongation of rete ridges and epidermal acanthosis(Fig. 2). We diagnosed this case as generalized pustular psoriasis(GPP). He responded with oral etretinate(50mg/day) and prednisone(60mg/day) over 6 days. His lesions nearly cleared in 4 weeks after continued administration of etretinate and prednisone at a lowered dosage. 5 weeks after antipsoriatic management, he developed new tense blisters on non-psoriatic skin regions of his lower extremities. A biopsy from perilesional skin showed subepidermal bulla with accumulation of neutrophils and eosinophils(Fig. 3). We considered the possibility of BP or EBA(epidermolysis bullosa

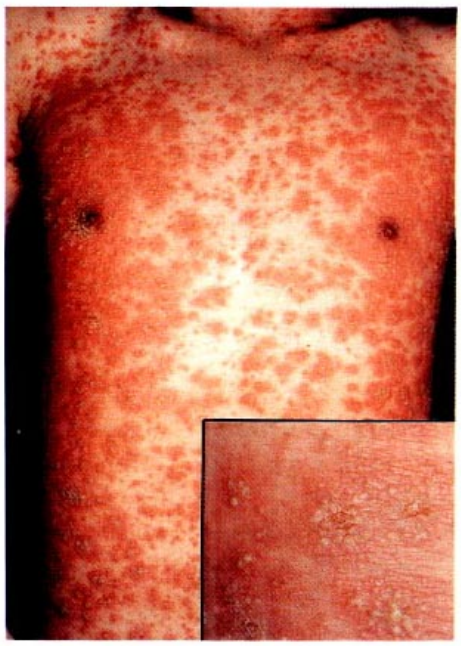

Fig. 1. Generalized scaling erythema and pustules all over his body in case 1.

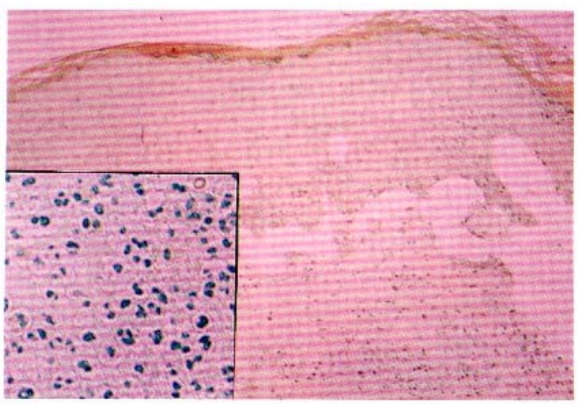

Fig. 3. Skin biopsy specimens from perilesional skin of case 1 showing subepidermal bulla with accumulation of neutrophils, eosinophils, nuclear dusts and fibrin in coagulum of bulla cavity(H & E, ×100(left), and × 400(right)).

acquisita). He responded poorly to prednisone and tetracycline but improved after switching to cyclosporine(5mg/kg/day, 300mg/day). The blistering eruption cleared in 4 weeks after administration of cyclosporine at a dose of 2 mg/kg/day. In the following year, cyclosporine was eventually stopped.

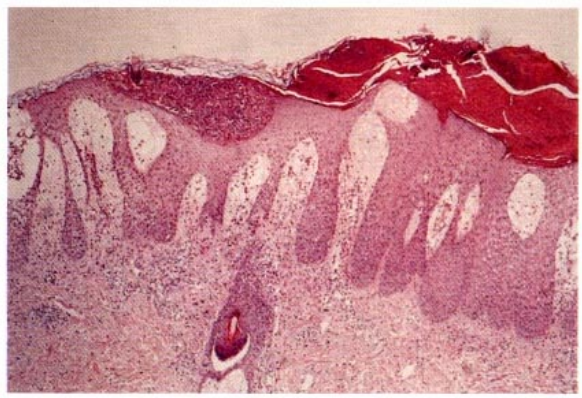

Fig. 2. Skin biopsy specimen showing intraepidermal spongiform pustules mainly filled with neutrophils, hyperkeratosis, parakeratosis, prominent elongation of rete ridges and epidermal acanthosis in case 1(H & E, ×100).

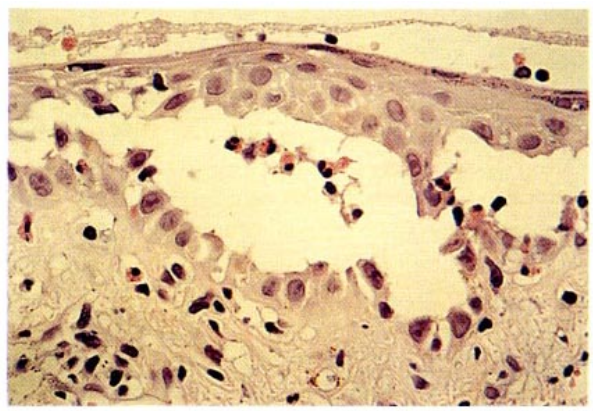

Fig. 4. Skin biopsy specimen from a bulla showing a suprabasal blister with mixed leukocytes, acantholytic keratinocytes, eosinophils, and epidermal regeneration in case 2(H & E, ×400).

Case 2

A 31-year-old man with an 8-year history of psoriasis vulgaris visited for the treatment of his worsening psoriasis. The patient's psoriasis had been treated only with topical steroids and calcipotriene ointment before his revisit. An examination disclosed scaly erythemas with 2-3 mm pustulopapules on his extremities. A skin biopsy from a pustule revealed typical findings, consistent with pustular psoriasis. At 3 weeks after starting therapy by etretinate and prednisone orally, the lesions evolved into a more intense flare of pustular psoriasis complicated by the onset of severe bullous eruptions on non-psoriatic regions. The flaccid

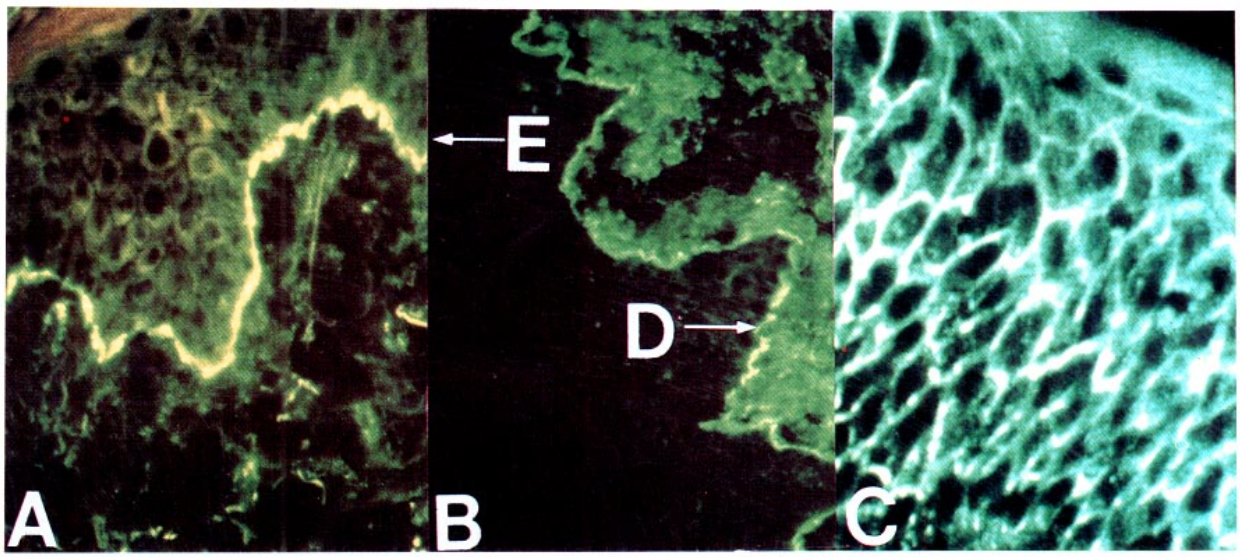

Fig. 5. DIF revealing linear deposition of IgG at the dermoepidermal junction in case 1(A, ×200). IIF using 1 mol/L salt-split human skin as a substrate, the IgG antibodies bound to the dermal side of the split in case 1(B, ×100, D: dermal side, E: epidermal side). DIF showing squamous intercellular deposition of IgG in the epidermis of case 2(C, ×200).

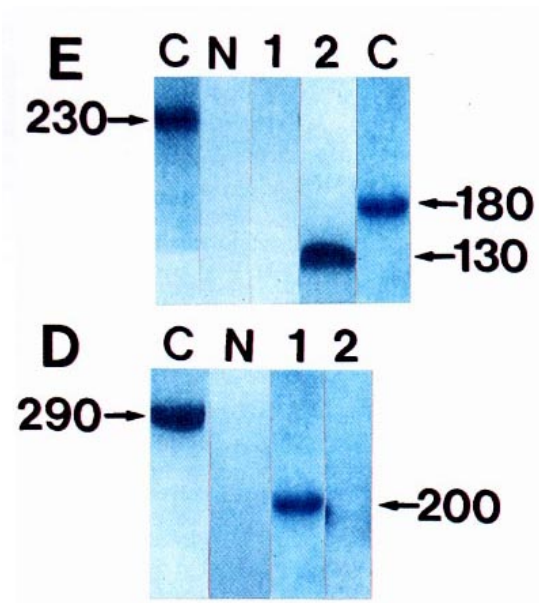

Fig. 6. On immunoblot analysis of epidermal extracts, the serum of case 2 reacted with the 130 kDa (desmoglein III) antigen. On immunoblotting of dermal extracts, the serum of case 1 reacted with 200 kDa protein(lane C: positive controls, lane N: negative normal controls, lane 1: case 1, lane 2: case 2, E: epidermal extract - 230 kDa BP antigen(BPAG1), 180 kDa BP antigen(BPAG2) and 130 kDa PV antigen (desmoglein III), D: dermal extracts - 290 kDa EBA antigen(type VII collgen).

blisters showed a lesional distribution on the anterior and posterior torso. A mucosal involvement in the oral cavity was also observed. Nikolsky's and Asboe-Hansen's signs were positive. A biopsy from the perilesional skin revealed a suprabasal blister with acantholytic keratinocytes, mixed leukocytes, eosinophils and cavitation of the upper epidermal layer by a regeneration process(Fig. 4). We diagnosed this case as pemphigus vulgaris(PV) combined with GPP. We treated him with cyclosporine 5mg/kg/day(300mg/day) combined with prednisone 60mg/day orally because he initially did not respond to oral prednisone alone. The blisters and psoriatic lesions cleared in 6 weeks by cyclosporine at a tapered dose of 3mg/kg/day. Approximately, 1 year later he had no blisters except mild psoriatic patches on his lower legs.

Immunofluorescence Studies

DIF was performed on perilesional sites of the two patients by a routine procedure[3,4]. The two patients' sera, sera from two patients with BP, confirmed by DIF, IIF, and Western immunoblotting, and sera from two normal people, were investigated by IIF on salt-split skin using a routine procedure. Split skin was obtained by incubating normal human skin in 1 mol/L NaCl for 24 hours at 4℃. Cryopre-

served 5 m thick skin sections were then incubated with the sera followed by an incubation with FITC-labelled rabbit-antihuman IgG or IgA antibody(DAKO, Copenhagen, Denmark). In case 1, DIF revealed linear deposition of IgG and C3 at the dermoepidermal junction(Fig. 5-A). There was no positiveness to IgA or IgM. IIF with patient's serum and a normal skin substrate demonstrated anti-BMZ IgG at a titer of 1:160. When 1 mol/L salt-split human skin was used as a substrate, the IgG antibodies were bound exclusively to the dermal side of the split(Fig. 5-B). In case 2, DIF revealed squamous intercellular deposition of IgG and C3(Fig. 5-C). IIF disclosed IgG anti-BMZ antibodies at a titer of 1:10.

Immunoblot Analysis

Immunoblot analysis was performed using EDTA-separated normal human epidermal extract for the detection of the 230 kDa BP antigen (BPAG1), the 180 kDa BP antigen(BPAG2) and the 130 kDa pemphigus vulgaris(PV) antigen (desmoglein III). EDTA-separated human dermal extracts were used for the detection of the 290 kDa EBA antigen(type VII collgen), as described previously[12-14,16]. Sera from patients with confirmed BP, EBA and PV were used as positive controls. All antigen sources were subjected to sodium dodecyl sulphate-polyacrylamide gel electrophoresis, and separated proteins were transferred electrophoretically to nitrocellulose sheets. Blots were blocked with 3% skimmed milk in Tris-HCl-buffered saline(TBS, pH 8.0), and incubated with sera diluted 1:40. After a wash with TBS containing 0.05% Tween 20, blots were incubated with peroxidase conjugated antihuman IgG(DAKO) at a dilution of 1:100. With immunoblotting of the epidermal extracts, the serum of case 2 reacted with the 130 kDa(desmoglein III) antigen. With immunoblotting of the dermal extracts, the serum of case 1 reacted with 200 kDa protein(Fig. 6).

DISCUSSION

There are many reports describing the coexistence of psoriasis and acquired autoimmune bullous dermatoses such as BP, PV, EBA, pemphigus foliaceus, pemphigus erythematosus and Hailey-Hailey disease[1-10]. However, the coexistence of generalized pustular psoriasis(GPP) and bullous disease as in our cases is quite rare[3]. Moreover, to date, there has been no report of the coexistence of the two diseases in Korea.

Because most previous studies were based on clinical findings, routine histopathological examinations, and DIF or IIF without more detailed investigations(e.g. immunoblot or IIF using salt-split technique or immunoelectron microscopic examination), it is unclear whether BP or PV or EBA associated with psoriasis was diagnosed correctly[5-7,9,10]. Nevertheless, most reports agreed that BP is a bullous disease most commonly associated with psoriasis[5-7]. However, several recent reports strongly posed the possibility that previously reported bullous disease accompanied by psoriasis might be a novel, atypical autoimmune blistering disease[3,4,8,11-14]. Saeki et al[3]. reported an unusual case of autoimmune blistering disease with anti-BMZ antibodies against an antigen other than BPAG1(230 kDa) or BPAG2(180 kDa) or EBA antigen(290 or 145 kDa). He suggested that the 210 and 200 kDa proteins might correspond to epiligrin or K-laminin as the culprit pathogenic autoantigens. As in our case 1, Chen et al[8]. concluded that the IgG autoantibodies against the novel 200 kDa lower lamina lucida target antigen seemed to participate in the pathogenesis of this unusual bullous dermatosis. Kirtschig et al[4]. also demonstrated a multiple, heterogenous antigen response in patients who had an acquired subepidermal disease, though his presented cases mostly reacted with BPAG1 or BPAG2. In our case 1, initially, BP or EBA had been considered through DIF, IIF, the salt-split technique, histopathological findings and clinical appearance. However, immunoblot analysis disclosed a third autoimmune blistering disease possessing unique autoantigens of 200 KDa. Compared with case 1, case 2 showed typical PV which could be confirmed by immunoblotting, demonstrating desmo-glein III(130 kDa).

In the pathogenetic explanation of the association of psoriasis and autoimmune bullous diseases, there are three hypotheses[3-10]; 1) a mechano-irritation effect of antipsoriatic management(e.g. tar, UVB, UVA, dithranol, excessive sun exposure, salicylic acid) may lead to a configurational alteration of the epidermal or dermal antigens to evoke an autoimmune reaction. BP lesions have actually been induced experimentally by irradiation of normal skin of BP patients with UVB[4]. 2) de no vo

changes at the BMZ in psoriasis inself may be responsible for triggering the bullous disease. Electron microscopic studies have shown a focal discontinuity and reduplication of the basal lamina in early psoriasis[4]. Therefore, the progression of psoriatic lesions can make the BMZ antigens unmasked or altered, leading to autoantibody production. 3) other endogenous factors such as metabolic errors in the degradation of epidermal components may result in binding of pre-existing autoantibodies[10]. However, the temporal relationship of the two diseases seems inconsistent. In most reported cases, psoriasis had started about 10 years before the evolution of bullous disease[3-8]. Conversely, bullous disease might precede the evolution of psoriasis[4]. In our case 1, extraordinarily, GPP without a personal history of previous psoriasis vulgaris nor family history, was followed by subepidermal blistering disease. In our case 2, psoriasis vulgaris was present 8 years prior to PV. Although in case 2, systemic steroid therapy might induce a flaring of GPP, steroids themselves did not seem to cause bullous disease directly. Moreover, our two cases had not been treated with topical or physical therapeutic modalities(e.g. tar, dithranol, UVB, PUVA) which might be suspected to be the inducers of bullous disease. Accordingly, at least in our cases, the association between psoriasis and autoimmune bullous disease seemed to be present basically as a result of immunological derangements that were not necessarily connected with the antipsoriatic treatment.

Regarding treatment, there are some dilemmas. Topical and physical treatment for psoriasis may provoke bullous lesions and systemic steroids for the treatment of bullous disease may cause a flare-up of the GPP after discontinuation[9,12]. Therefore, cyclosporine, dapsone, colchicine, and methotrexate, have been recently highlighted as an alternative or even primary therapy for these enigmatically coexisting diseases[9,13-15]. Our two patients were treated with low doses of cyclosporine without notifiable adverse effects nor rebound phenomena after discontinuation.

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