Two Cases of Anti-Epiligrin Cicatricial Pemphigoid With and Without Associated Malignancy

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**Case Reports**

**Case 1**

A 90-year-old Japanese man presented with recurrent erosions on the buccal mucosa, nasal meatus, trunk and extremities (Fig. 1a). Laryngoscopy revealed a white coating around the epiglottis, but not laryngeal stenosis. He showed symblepharon of both eyes and corneal perforation of the left eye (Fig. 1b). He had rheumatoid arthritis, diabetes mellitus and prostate carcinoma. The latter had been diagnosed one year before the blistering. The histological diagnosis of the prostate carcinoma was poorly differentiated adenocarcinoma (Gleason score 9). A blood test for prostate specific antigen (PSA) gave a result of 100 ng/ml (normal < 4 ng/ml). Following treatment with leuprorelin acetate monthly, his PSA level decreased to normal and an abnormal level was not recorded during the following 3 years. Skin biopsy of the lower leg revealed a subepidermal blister with an infiltration of eosinophils and neutrophils (Fig. 1c). Direct immunofluorescence demonstrated linear deposits of IgG and C3 at the basement membrane zone of the epidermis (Fig. 1d). Indirect immunofluorescence demonstrated circulating IgG anti-basement membrane auto-antibodies that bound to the dermal side of 1M NaCl split normal skin (Fig. 1e). Immunoblotting using laminin 5 purified from keratinocyte extract as a substrate showed that the IgG antibodies of patient 1 reacted with the 140-kDa β3 subunit of laminin 5 and IgG antibodies of patient 2 reacted with the 165-kDa and 145-kDa α3 subunits. Patient 1 had prostate carcinoma and his blistering was resistant to therapy. Patient 2 had no detectable malignancy and treatment with doxycycline gave a successful response.
the number of blisters decreased, new blister formation persisted. Additional oral dapsone, 100 mg daily, produced a slower response. Computed tomography of the whole body, ultrasonography of the abdomen and gastric endoscopy revealed no detectable malignant lesion.

Case 2

A 69-year-old Japanese woman presented with recurrent erosions and a white coating on the larynx and nose with trachyphonia and dyspnoea. The lesions healed with scarring (Fig. 3a). She also developed blistering of the trunk and lower legs (Fig. 3b). Skin biopsy of the trunk revealed a subepidermal blister with an infiltration of eosinophils and neutrophils (Fig. 3c). Direct immunofluorescence demonstrated linear deposits of IgG at the basement membrane zone of the epidermis (arrows). (e) Indirect immunofluorescence demonstrated circulating IgG anti-basement membrane zone auto-antibodies that bound to the dermal side of 1M NaCl split normal skin (arrows). Positivity of epidermis is non-specific staining.

Fig. 1. Clinical features and histological and immunopathological findings of patient 1. (a) Recurrent erosions on the trunk and extremities. (b) Symblepharon. (c) Skin biopsy from the lower leg revealed a subepidermal blister with an infiltration of eosinophils and neutrophils. Bar = 100 µm. (d) Direct immunofluorescence demonstrated a linear deposit of IgG at the basement membrane zone of the epidermis (arrows). (e) Indirect immunofluorescence demonstrated circulating IgG anti-basement membrane zone auto-antibodies that bound to the dermal side of 1M NaCl split normal skin (arrows). Positivity of epidermis is non-specific staining.

Fig. 2. Immunoblotting using laminin 5 purified from keratinocyte extract as the substrate for patient 1 showed that the IgG antibodies reacted with 140-kDa polypeptides identical to the β3 subunit of the laminin 5 molecule.

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the medication due to vertigo and nausea. She was therefore treated with doxycycline hydrochloride 100 mg, and nicotinamide 1500 mg daily. The erosions on the laryngeal mucosa and blistering of the skin improved gradually in response to this treatment. Although the stenosis of her vocal chink and trachyphonia did not improve, the breathing difficulty resolved. We searched for underlying occult cancer in this patient, but did not detect any malignancy. She showed no malignancy when followed up for 3 years.

DISCUSSION

AECP is a chronic, autoimmune, mucous membrane-dominated, subepithelial blistering disease that occurs with equal frequency in men and women. Current estimates suggest that it comprises 5–20% of cases of mucous membrane pemphigoid (1).

Recent studies have shown that people with AECP have an increased relative risk for malignant tumours (1–3). Sadler et al. (2) reviewed 15 cases of AECP associated with cancers. Five cases had lung cancers, three had stomach cancers, two had colon cancers, two had endometrial cancers and one had ovarian cancer as solid tumours. Two cases had lymphomas. In 12 of 15 patients, the time between blister onset and cancer diagnosis was under 14 months. Patient 1 in this report is the first published case of AECP associated with prostate carcinoma. The prostate carcinoma was diagnosed one year before the onset of blistering.

Egan et al. (3) calculated the expected numbers of cancers in a cohort of 35 patients with AECP in the National Cancer Institute’s Surveillance, Epidemiology, and End Results (NCI SEER) Registry. Ten of these patients (28.6%) had solid cancers and the relative risk for malignancy in this cohort was 6.8, similar to the risk for malignancy among patients with dermatomyositis. Similarly, Matsushima et al. (5) reviewed 16 cases of AECP in Japan and 5 of these cases (31.2%) were complicated with solid cancers.

Some experimental studies have demonstrated that AECP is a distinct disorder mediated by tissue-specific, pathogenic auto-antibodies against laminin 5 (6–9). Laminin 5 (α3β3γ2) is a heterotrimeric protein of 460 kDa. Laminin 5 is a major adhesive component of epidermal basement membrane zone. In the skin, laminin 5 is localized to the interface of lamina lucida and the lamina densa, where it is thought to form a critical link between hemidesmosome-anchoring filament complexes, the lamina densa and underlying anchoring fibrils (10).
The mechanism underlying the association of AECP and cancer is not fully understood, but there is emerging evidence that laminin 5 expression in cancer cells promotes their growth, invasion and metastasis (11). However, some studies showed controversial data. Hao et al. (12) reported invasive prostate carcinoma showing a loss of expression of α3 and γ2 subunits of laminin 5 with variable expression of α3 subunit. Nevertheless, Taniuchi et al. (13) reported an interesting case of AECP associated with gastric carcinoma. The gastric carcinoma cells in the patient produced laminin 5 and the patient’s serum contained auto-antibodies against laminin 5. Furthermore, the blistering symptoms and titre of anti-basement membrane zone antibodies co-ordinately changed with the resection and subsequent relapse of the gastric cancer.

Patients who present with mucous membrane pemphigoid, anti-laminin 5 auto-antibodies should be checked, and careful screening for internal malignancies should be performed in cases that are positive for anti-laminin 5 antibodies.

AECP is a chronic, insidiously progressive disease with a high mortality rate. Mortality is especially high in AECP patients who develop solid cancers in close proximity to the time of blister onset. Egan et al. (1) reported that 14 of 35 (40%) patients died during the follow-up period. Eight patients died from cancer, and 4 of the remaining 6 deaths were due to infections that developed during intensive treatment with immunosuppressives. The combined therapy of tetracycline and nicotinamide was reported as an effective treatment for various types of cicatricial pemphigoid (14). Patient 2 in this report, who had no detectable malignancy, was treated successfully with doxycycline and nicotinamide. For patients in whom immunosuppressive medication cannot be used in the treatment of AECP, treatment with doxycycline and nicotinamide should be considered.

REFERENCES