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Mucous Membrane Pemphigoid with Antibodies to the β_3 Subunit of Laminin 332 in a Patient with Acute Myeloblastic Leukemia and Graft-versus-Host Disease

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Key Words

Laminin 332 • Mucous membrane pemphigoid • Leukemia • Graft-versus-host disease

Introduction

Mucous membrane pemphigoid (MMP), formerly termed cicatricial pemphigoid, is a heterogeneous group of autoimmune subepithelial blistering diseases that mainly affect mucous membranes, such as the oral, conjunctival, nasal, pharyngeal, laryngeal, esophageal and anogenital mucosae, leading to scarring of the affected tissue [1]. Laminin 332 (previously termed laminin 5, epiligrin, kalinin or nicein), located in the epidermal basement membrane zone, has been characterized as a heterotrimeric glycoprotein consisting of α_3 , β_3 and γ_2 subunits that are covalently linked by disulfide bonds [2]. Patients with one form of MMP have pathogenic autoantibodies against laminin 332. Immunoblotting studies using extracts of cultured keratinocytes revealed that a majority of anti-laminin-332 MMP sera reacted with the α_3 subunit [3, 4] and some with the γ_2 subunit [5]. In this report we describe an unusual case of MMP with antibodies to only the β_3 subunit of laminin 332, who had acute myeloblastic leukemia (AML) and graft-versus-host disease (GVHD).

Case Report

A 35-year-old female visited our hospital for treatment of AML and received chemotherapy and a bone marrow transplantation (BMT) from a human-leukocyte-antigen-matched unrelated donor in May 2005. She developed red papules and small erythemas on the face and extremities 2 weeks after the BMT. A biopsy was performed, and a diagnosis of GVHD was made. GVHD was well controlled by treatment with oral tacrolimus. In November 2005, when relapse of AML was detected by PCR, multiple blisters appeared in the perioral region, and tacrolimus was discontinued. She received antibiotics and acyclovir under the di-

Fig. 1. Clinical features of the patient. Blisters and erosions were seen on the face and oral mucosa.

agnosis of impetigo and/or herpes virus infection, while blisters and erosions developed in the oral mucosa and over the face and neck (fig. 1). There was no erosion or blister in the conjunctival, nasal or pharyngeal mucosae. She did not have any other apparent skin lesion caused by GVHD. A biopsy specimen revealed a sub-epidermal blister containing eosinophils and neutrophils (fig. 2a). Direct immunofluorescence demonstrated a linear deposition of IgG and C3 in the basement membrane zone of the epidermis (fig. 2b). Indirect immunofluorescence revealed weak IgG anti-basement-membrane-zone antibodies which reacted with the dermal side of 1 M NaCl-split skin.

By immunoblotting of normal human epidermal extracts, the serum of this patient reacted weakly with the 230-kDa bullous pemphigoid (BP) antigen (BP230) and the 190-kDa periplakin. The significance of these reactivities remains unclear. Immunoblotting of normal human dermal extracts showed no apparent reactivity with the serum of this patient. Immunoblotting using laminin 332 purified from human cultured keratinocytes showed that this patient's serum reacted strongly with the 140-kDa β_3 subunit, but not with the α_3 or γ_2 subunit (fig. 3). Based on these findings, she was diagnosed as having anti-laminin-332 MMP. Based on a tentative diagnosis of BP, treatment had been initiated with oral minocycline 200 mg and topical steroid before the final diagnosis of MMP was made. Although the number of blisters decreased, new blister formation persisted. Three weeks later, the number of blood leukemic cells started to increase rapidly, and she decided to receive cord blood transplantation. However, she died of disease progression after early relapse.

Fig. 2. **a** A biopsy specimen revealed a subepidermal blister containing eosinophils and neutrophils. **b** Direct immunofluorescence demonstrated a linear deposition of IgG on the basement membrane zone of the epidermis.

Fig. 3. **a** By immunoblotting of normal human epidermal extracts, the control pemphigus vulgaris (PV) serum reacted with the 160-kDa desmoglein 1 and the 130-kDa desmoglein 3 (lane 1), the control paraneoplastic pemphigus (PNP) serum reacted with the 210-kDa envoplakin and the 190-kDa periplakin (lane 2), and the control BP serum reacted with BP230 and BP180 (lane 3). The serum of our patient reacted relatively weakly with BP230 and the 190-kDa periplakin (lane 4). **b** By immunoblotting of normal human dermal extracts, the control epidermolysis bullosa acquisita (EBA)

serum reacted with the 290-kDa type VII collagen (lane 1), and the anti-p200 pemphigoid serum (p200) reacted with the 200-kDa antigen (lane 2). The serum of our patient showed only a faint reactivity with a protein of about 250 kDa (lane 3). **c** By immunoblotting of purified human laminin 332, control anti-laminin-332 MMP serum reacted with the 165-kDa α_3 , the 145-kDa α_3 , the 140-kDa β_3 and the 105-kDa γ_2 subunits (lane 1). A normal control serum showed no reactivity (lane 2). Our patient's serum reacted strongly and exclusively with the 140-kDa β_3 subunit (lane 3).

Discussion

The present case possessed autoantibodies to only the β_3 subunit of laminin 332, which is unusual, but reported in a few cases [6–10]. The previous report includes the case of a 72-year-old Caucasian man with blisters and erythema all over the skin, and erosions in the conjunctiva, mouth and larynx [9]. He had metastatic adenocarcinoma of unknown origin in the lymph nodes of the neck. He died of respiratory failure due to laryngeal obstruction as a result of blister formation. Seo et al. [7] reported the case of a 67-year-old Korean woman with erosions in the oral and conjunctival mucosae with laryngeal and esophageal involvement. She also had cutaneous blisters and erosions on the trunk. She was successfully treated with a combination of prednisolone 50 mg/day and cyclophosphamide 50 mg/day. There was no evidence of associated neoplasm. Fukushima et al. [6] reported the case of a 90-year-old Japanese man with erosions on the oral, nasal, conjunctival mucosae, trunk and extremities. He had prostate carcinoma (poorly differentiated adenocarcinoma). The other two reports have no clinical information [8, 10]. Therefore, the differences between this form and the other forms of MMP in the clinical features, prognosis and complications are not apparent at the present time.

Initially, a diagnosis of BP was also considered because the patient had cutaneous bullae and erythemas. However, the presence of head and neck involvement and the presence of mucosal involvement do not generally support the diagnosis of BP [11]. Furthermore, autoantibodies to laminin 332 had been confirmed previously to be a specific marker of MMP [12]. Therefore, the diagnosis of anti-laminin-332 MMP was considered appropriate, based on the results of the immunoblotting studies. A reactivity against 210- and 190-kDa epidermal proteins corresponding to envoplakin and periplakin, respectively, is found in patients with paraneoplastic pemphigus. However, the histological and immunopathological findings were not consistent with this diagnosis.

It has been shown that autoimmune blistering diseases such as BP may be associated with internal malignancies [13]. Thus, anti-laminin-332 MMP has been shown to have a much higher risk for solid cancers, such as lung, gastric and colon cancers [14, 15], although the clinical features are similar to those of the other forms of MMP. Egan et al. [14] reported that 10 of 35 patients had solid cancers in a United States National Cancer Institute Surveillance, and Matsushima et al. [15] reviewed Japanese cases and showed that 5 of 16 cases of anti-laminin-332 MMP were complicated with solid cancers. However, a possible association of anti-laminin-332 MMP with a hematological neoplasm such as AML has not been clarified. Aisa et al. [16] reported a case of anti-BP230 MMP with follicular lymphoma treated with peripheral blood stem cell transplantation without any obvious chronic GVHD.

GVHD is one of the major complications after hematopoietic stem cell transplantations and critically induced and maintained by donor immunocompetent cells that attack epithelia of fast proliferating tissues [17]. The present case did not have any clinical findings indicating chronic GVHD at the onset of MMP. However, it might be possible that undiscovered slight attacks of GVHD triggered these cases of MMP, since more than 10 cases of autoimmune blistering diseases, mostly BP, after allogeneic BMT have been reported to date [18, 19]. Indeed, various autoimmune diseases, including vitiligo, have been shown to develop in patients with GVHD [20, 21], although the mechanism is unknown. It is possible that some cases may stem from donor-related trans-

fer of pathogenic lymphocytes (autoreactive B cells against laminin 332 in our case) or their progenitors, while most of the cases can be attributed to the immunological imbalances after BMT [20].

Thus, the diagnosis of autoimmune blistering disease, including MMP, should be considered when bullous or erosive lesions are found on the skin and mucosa in patients with leukemia and/or GVHD.

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