Concurrence of Autoantibodies to Both Laminin γ1 and γ2 Subunits in a Patient with Kidney Rejection Response

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Accepted March 12, 2012.

Anti-laminin γ1 pemphigoid and anti-laminin-332 mucous membrane pemphigoid (MMP) are two distinct autoimmune blistering diseases. Anti-laminin γ1 pemphigoid is characterized by autoantibodies to a 200-kDa acidic non-collagenous glycoprotein of the lower lamina lucida, while anti-laminin-332 MMP is characterized by autoantibodies to various subunits of laminin-332 of the basement membrane. We report here an extremely rare case of pemphigoid with autoantibodies to both laminin γ1 and the γ2 subunit of laminin-332, which developed following the rejection response to the transplanted kidney.

CASE REPORT

A 61-year-old Japanese man presented to our hospital in November 2009 with fever of unknown origin, multiple blisters without rupture and erosions of the oral mucosa, including the palate, tongue, and buccal mucosa, and a tense blood blister (38×38 mm) on the left cubital region (Fig. 1a, b, c). He had a past medical history of living-donor kidney transplantation for the treatment of immunoglobulin A nephropathy in June 2006. After the renal transplantation, he was making satisfactory progress by oral administration of immunosuppressants including cyclosporin A (70 mg/day), prednisolone (7.5 mg/day), and mizoribine (75 mg/day). However, in January 2009, he chose to stop taking these immunosuppressive agents. Starting in August 2009, he had a persistent fever of 38ºC to 39ºC and was admitted to our hospital. Histopathological findings of a biopsy specimen from a bullous lesion of the tongue revealed subepithelial blistering with marked infiltration of lymphocytes and neutrophils and granulation with remarkable angiogenesis (Fig. 1d, e). Direct immunofluorescence showed linear deposition of C3 at the basement membrane zone (BMZ) of the oral mucosa (Fig. 1f), but not of IgA, IgG, or IgM (data not shown). Indirect immunofluorescence (IIF) for IgA and IgG was negative on both the epidermal cell surface and BMZ. IIF on 1 M NaCl split-skin detected linear IgG deposition in the dermal side. In immunoblotting analyses using human dermal extracts, the serum of this patient reacted with the 200-kDa laminin γ1 (Fig. 2b). Furthermore, immunoblotting analyses with purified human laminin-332 showed IgG autoantibodies of the patient bound to the 105-kDa protein, corresponding to the γ2 subunit of laminin-332 (Fig. 2c). After administration of mycophenolate mofetil (500 mg/day), tacrolimus (5 mg/day), and methylprednisolone (8 mg/day) for the rejection response to the transplanted kidney, the fever subsided quickly and blood blister on the left cubital region had completely disappeared 2 months later. The blisters of the oral mucosa also completely disappeared after the use of dexamethasone solution mouthwash. In this case, steroid therapy with immunosuppressive agents was applied successfully for treatment of the rejection response to the transplanted kidney and the pemphigoid.

DISCUSSION

Two unusual cases of anti-laminin γ1 pemphigoid with predominant involvement of mucous membranes have been reported (1, 2). One was a patient who suddenly developed tense blisters of the vulvar and oral mucosal membranes and pruritic vesicles involving both palms. The other was a case of metastatic ovarian carcinoma-associated subepidermal blistering disease

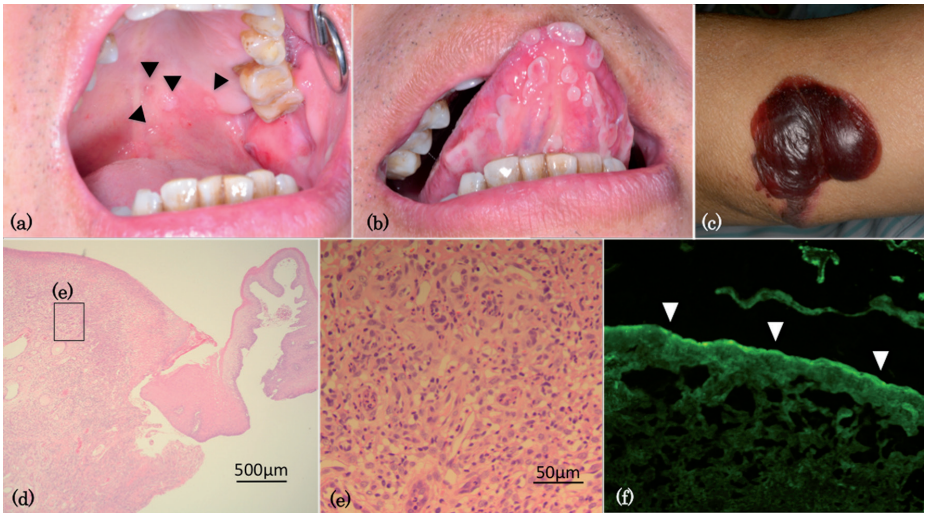

Fig. 1. Clinical findings at first visit. (a) Multiple blisters in the palatal mucosa and (b) lingual mucosa. (c) A tense blood blister on the left cubital region. (d) Histopathological findings of a bullous lesion of the tongue (haematoxylin-eosin). (e) Marked lymphocytic infiltration and granulation formation with remarkable angiogenesis. (f) Direct immunofluorescence showed linear deposition of C3 at the basement membrane zone of the oral mucosa.

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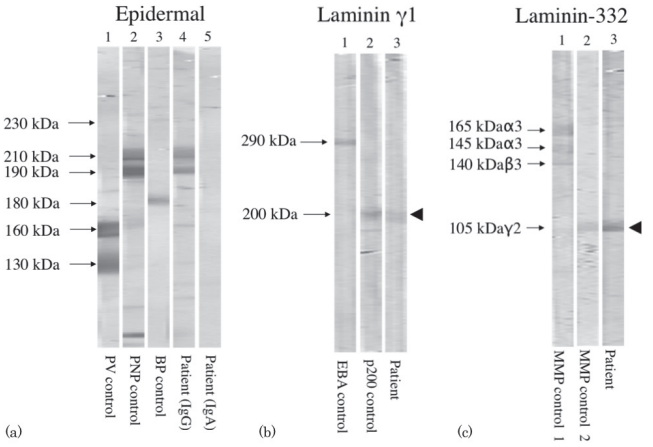

Fig. 2. Immunoblotting analyses. (a) With epidermal extracts, control pemphigus vulgaris (PV) serum reacted with the 160-kDa (Dsg1) and the 130-kDa (Dsg3) (*lane 1*), control paraneoplastic pemphigus (PNP) serum reacted with the 210-kDa envoplakin and the 190-kDa periplakin (*lane 2*), and control bullous pemphigoid (BP) serum reacted with BP230 and BP180 (*lane 3*). IgG antibodies of this patient reacted with envoplakin and periplakin (*lane 4*). IgA antibodies of this patient showed no reaction. (b) With dermal extracts, control epidermolysis bullosa acquisita (EBA) serum reacted with the 290-kDa protein (*lane 1*) and control anti-laminin γ1 (p200) pemphigoid serum reacted with the 200-kDa (*lane 2*). IgG antibodies in the serum of our patient reacted to the laminin γ1 antigen. (c) With purified laminin-332, control MMP serum reacted with the 165-kDa α3, the 145-kDa α3, the 140-kDa β3, and the 105-kDa γ2 subunits (*lanes 1 and 2*). IgG antibodies from this patient reacted with the γ2 subunit of laminin-332 (*lane 3*).

with severe blisters and erosions on multiple mucous membranes including lip, oral cavity, nose, eye, genitalia, and anus. In these 2 patients, immunoblotting analyses demonstrated the presence of autoantibodies against both laminin γ1 and laminin-332, as in our case. Similarly, it has been reported that anti-p200 pemphigoid sera contained other target antigens of the dermal–epidermal junction, such as BP180 (3–7), BP230 (4, 7, 8), the α3 chain of laminin 332 (1) and the type VII collagen (9, 10).

A high degree of sequence homology is observed between laminin γ1 and laminin-332 γ2 (34% identity and 27% similarity; Blastp Align, NCBI). Therefore it is possible that the unusual autoimmune profile of this case also developed as a result of epitope spreading. Alternatively, it may have resulted from immune dysregulation by the rejection response to the transplanted kidney, and autoantibodies against multiple components of the BMZ might have been simultaneously and independently produced.

Laminin-332 is highly expressed in many types of solid cancers. Therefore, it is considered that pemphigoid with autoantibodies to laminin-332 may be closely related to malignant tumours (11). Matsushima et al. (12) reported that 5 of 16 cases of anti-laminin-332 MMP were complicated with solid cancers. We thus remain alert to the development of cancer.

Interestingly, in this case, the presence of IgG autoantibodies to target antigens of paraneoplastic pemphigus, envoplakin, and periplakin was also confirmed by immunoblotting analyses. However, IgG deposition was not observed by IIF using rat urinary bladder specimens, and anti-envoplakin and anti-periplakin autoantibodies were not detected by enzyme-linked immunosorbent assay. Further studies are necessary to examine whether multiple different autoantibodies are closely associated with the different phenotypes and disease severity of pemphigoid.

The authors declare no conflicts of interest.

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