# Symmetrical Skin Lesions on the Gluteal Region in a Patient with Anti-Laminin-332 Mucous Membrane Pemphigoid

Mucous membrane pemphigoid (MMP), previously called cicatricial pemphigoid, is a rare subepidermal immunobullous disorder that primarily affects the mucous membranes (1,2). MMP is divided into two major subtypes, anti-BP180-type MMP and anti-laminin-332 (previously called laminin 5 or epiligrin) MMP. Anti-laminin-332 MMP is known to be associated with malignant tumors (3), which may cause overexpression of autoantibodies and induce autoimmunity to laminin-332 (4). MMP primarily affects the mucous membranes, and widespread skin lesions are rare. In MMP, circumscribed skin lesions have been previously reported as occurring on the head, neck, and upper trunk (5). We report a case of anti-laminin-332 MMP presenting with symmetrical skin lesions characteristic of MMP on the weight-bearing areas of the gluteal region.

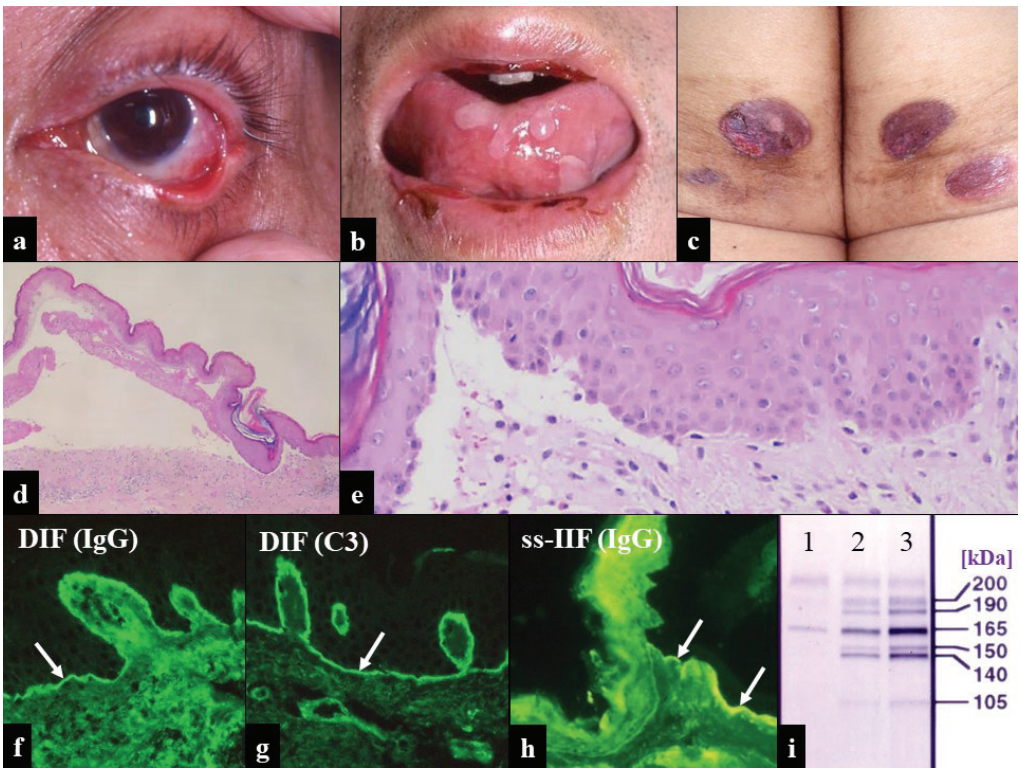


**Figure 1.** Clinical, histopathologic, and immunologic findings in the present case. (a) Hyperemic conjunctiva and adhesion in the left eye. (b) Tense bullae on the tongue and erosions on the lips. (c) Ruptured blisters with erosions on an erythematous base on the weight-bearing areas of the gluteal region. (d, e) Histopathologic features of a subepidermal blister with lymphocytic and eosinophilic infiltrates; hematoxylin-eosin stain, (d) ×40, (e) ×200). (f, g) Direct immunofluorescence showing basement membrane zone deposition of IgG and C3 (f, g) ×400x. (h) Indirect immunofluorescence on 1 mol/L NaCl-split skin showing IgG reactivity on the dermal side of the split (×200). Positive reactivity in immunofluorescence is indicated by white arrows. (i) Immunoprecipitation using radio-labeled cultured keratinocyte lysate. The control with anti-laminin-332-type mucous membrane pemphigoid (lane 2) and our patient (lane 3), but not the normal control (lane 1), show positive reactivity with laminin-332.

A 66-year-old Japanese man presented with a month-long history of multiple erosions and blisters on the mucous membranes and skin, with conjunctival hyperemia, nasal obstruction, oral pain, and hoarseness of voice. Three days before the first visit, he was diagnosed with gastric cancer with liver metastasis by gastrointestinal endoscopy and abdominal ultrasound examination for tarry stool.

Physical examination demonstrated erosions and tense bullae on the conjunctivae, tongue, and lips (Figure 1, a,b), as well as erosive erythematous skin lesions on the nape, right index finger, both legs, and symmetric lesions on the gluteal region (Figure 1, c). His body weight was 86 kg. Laboratory examinations showed slight liver dysfunction and elevation of C-reactive protein levels. Histopathologic examination of the skin lesions demonstrated subepidermal blisters with lymphocytic and eosinophilic infiltrates (Figure 1, d,e).

Direct immunofluorescence (IF) revealed linear deposits of IgG and C3, but not IgA, along the basement membrane zone (BMZ) (Figure 1, f,g). An IgG subclass study showed $IgG_1$ and $IgG_4$ deposits. Indirect IF on normal human skin revealed weak positivity for IgA anti-keratinocyte cell surface antibodies and IgG anti-BMZ antibodies, which were bound to the dermal side of 1 mol/L NaCl-split skin (Figure 1, h). IgG immunoblot analyses of both normal human epidermal and dermal extracts showed negative results (including BP230, BP180, 290 kDa type VII collagen, and 200 kDa laminin-γ1). Immunoprecipitation using radio-labeled cultured keratinocyte lysate demonstrated positive reactivity with laminin-332 (Figure 1, i).

We established the diagnosis of anti-laminin-332 MMP. We started treatment with oral minocycline (200 mg/day) and niacinamide (900 mg/day) with topical corticosteroids without any effect after 2 weeks of therapy. Administration of oral prednisolone (40 mg/day) with topical corticosteroids and alprostadil ointment on the skin lesions, as well as beclometasone dipropionate powder on the oral lesions resulted in significant improvement of mucocutaneous lesions within 10 days. Although the gastric cancer and liver metastasis initially responded to chemotherapy with fluorouracil and cisplatin, the patient succumbed to multiple organ failure 9 months after the initial visit.

Anti-laminin-332 antibodies were originally detected by immunoprecipitation, as in our case. Immunoblotting of purified human laminin-332 have been subsequently developed, which detects the 165/145 kDa α3, 140 kDa β3, and 105 kDa γ2 subunits of laminin-332 in various patterns (6). Today, the ELISA system uses laminin-332 preparations as adjunct diagnostic tools in MMP (7).

Occasionally, a wide spectrum of autoantibodies is detected in MMP, for example, MMP with IgG antibodies to both BP180 and laminin-332, which were considered to be developed via epitope spreading. Detection of circulating IgA autoantibodies against the skin have also been reported in MMP (8). However, the pathogenic significance and mechanisms of coexistence of IgG anti-laminin-332 antibodies and IgA anti-keratinocyte cell surface antibodies found in our case are currently unknown.

It is generally considered that $IgG_1$ antibodies activate complements and are pathogenic in MMP, while $IgG_4$ antibodies behave as blocking antibodies and are protective. In our case, direct IF revealed $IgG_1$ and $IgG_4$ deposits; the same was reported in a previous case report (9). The pathogenic roles of autoantibodies with different IgG subclasses need to be analyzed in further studies. Conjunctival mucosal lesions in MMP may occur by rubbing of the eyes due to irritation. Blinking subjects the conjunctivae to repeated friction. Vocal cords vibrate during breathing and speaking. The tongue moves while eating and drinking; in particular, the tip of the tongue gets into frequent contact with the inner sides of the incisor teeth. In the present case, characteristic symmetrical skin lesions were seen on the weight-bearing areas of the gluteal region on bony prominences which receive mechanical stresses in the sitting position. These skin lesions were subjected to repeated stretch and pressure stresses, but no ischemic changes were observed, such as decubitus ulcers. Therefore, the symmetrical skin lesions in the gluteal region as well as the ocular and oral mucosal lesions seen in our patient might have resulted from the same mechanism of pathogenesis.

We reported a case of anti-laminin-332 MMP presenting with symmetrical gluteal skin lesions, probably induced by mechanical stress. MMP primarily affects the mucous membranes, and widespread skin lesions are rare. Our case emphasizes that clinicians need to specifically check for the presence of skin lesions on weight-bearing parts of the body during examination of patients with suspected MMP.

## Acknowledgements:

We gratefully appreciate Dr. Kim B. Yancey (University of Texas Southwestern Medical Center, Dallas, TX 75390-9069, USA) for performing the serum analysis in our case.

## Conflict of interest:

There were no conflicts of interest.

## References:

1. Chan LS, Ahmed AR, Anhalt GJ, Bernauer W, Cooper KD, Elder MJ, et al. The first international consensus on mucous membrane pemphigoid: definition, diagnostic criteria, pathogenic factors, medical treatment, and prognostic indicators. Arch Dermatol. 2002;138:370-9.
2. Yancey KB, Kirtschig G, Yee C, Lazarova Z. Studies of patients with anti-epiligrin cicatricial pemphigoid. J Dermatol. 1995;22:829-35.
3. Egan CA, Lazarova Z, Darling TN, Yee C, Coté T, Yancey KB. Anti-epiligrin cicatricial pemphigoid and relative risk for cancer. Lancet. 2001;357:1850-1.
4. Koshikawa N, Moriyama K, Takamura H, Mizushima H, Nagashima Y, Yanoma S, et al. Overexpression of laminin γ2 chain monomer in invading gastric carcinoma cells. Cancer Res. 1999;59:5596-601.
5. Amber KT, Murrell DF, Schmidt E, Joly P, Borradori L. Autoimmune subepidermal bullous diseases of the skin and mucosae: clinical features, diagnosis, and management. Clin Rev Allergy Immunol. 2018;54:26-51.
6. Hisamatsu Y, Nishiyama T, Amano S, Matsui C, Ghohestani R, Hashimoto T. Usefulness of immunoblotting using purified laminin 5 in the diagnosis of anti-laminin 5 cicatricial pemphigoid. J Dermatol Sci. 2003;33:113-9.
7. Chiorean R, Danescu S, Virtic O, Mustafa MB, Baican A, Lischka A, et al. Molecular diagnosis of anti-laminin 332 (epiligrin) mucous membrane pemphigoid. Orphanet J Rare Dis. 2018;13:111.
8. Cozzani E, Drosera M, Parodi A, Carrozzo M, Gandolfo S, Rebora A. Frequency of IgA antibodies in pemphigus, bullous pemphigoid and mucous membrane pemphigoid. Acta Derm Venereol. 2004;84:381-4.
9. Hsu R, Lazarova Z, Yee C, Yancey KB. Noncomplement fixing, $IgG_4$ autoantibodies predominate in patients with anti-epiligrin cicatricial pemphigoid. J Invest Dermatol. 1997;109:557-61.

**Nobuki Maki[1], Toshio Demitsu[2], Hajime Nagato[3], Osamu Okada[4], Kozo Yoneda[5], Takashi Hashimoto[6], Naoko Hasunuma[7], Shin-Ichi Osada[8], Motomu Manabe[1]**

*[1]Department of Dermatology, Akita National Hospital, Akita, Japan*

*[2]Department of Dermatology, Jichi Medical University Saitama Medical Center, Saitama, Japan*

*[3]Nagato Dermatology Clinic, Chiba, Japan*

*[4]Okada Dermatological Clinic, Akita, Japan*

*[5]Department of Clinical Pharmacology, Faculty of Pharmaceutical Sciences, Osaka Ohtani University, Osaka, Japan*

*[6]Department of Dermatology, Osaka City University Graduate School of Medicine, Osaka, Japan*

*[7]Department of Medical Education, Graduate School of Biochemical and Health Sciences, Hiroshima University, Hiroshima, Japan*

*[8]Department of Dermatology, Nippon Medical School Tama Nagayama Hospital, Tokyo, Japan*

**Corresponding author:**

Nobuki Maki; MD

Department of Dermatology

Akita National Hospital,

84-40 Idonosawa

Iwakiuchimichikawa, Yurihonjo,

Akita 018-1393

Japan.

*maki.nobuki.mc@mail.hosp.go.jp*

Received: December 27, 2020

Accepted: June 15, 2021