

SHORT COMMUNICATION

Mucous Membrane Pemphigoid with IgG Autoantibodies to the 120-kDa Ectodomain of Type XVII Collagen (BP180/Linear IgA Dermatitis Antigen) in a Patient with Idiopathic Thrombocytopenic PurpuraYuka Hirakawa¹, Naoki Oiso¹, Norito Ishii², Hiroshi Koga², Megumi Tatebayashi¹, Shusuke Uchida¹, Hiromasa Matsuda¹, Takashi Hashimoto² and Akira Kawada¹*Departments of Dermatology, ¹Kinki University Faculty of Medicine, 377-2 Ohno-Higashi, Osaka-Sayama, Osaka 589-8511 and ²Kurume University School of Medicine, and Kurume University Institute of Cutaneous Cell Biology, Kurume, Japan. E-mail: hirakawa@med.kindai.ac.jp**Accepted Sep 1, 2014; Epub ahead of print Sep 2, 2014*

Mucous membrane pemphigoid (MMP) is an autoimmune subepidermal blistering disease involving primarily the mucosae and occasionally the skin (1–3). We report here a case of a Japanese male patient with idiopathic thrombocytopenic purpura (ITP) who later developed MMP with IgG autoantibodies to the 120-kDa soluble ectodomain of type XVII collagen (BP180) (linear IgA dermatosis antigen; LAD-1).

CASE REPORT

A 72-year-old Japanese man was referred to us in December 2013 with progressive mucocutaneous blistering lesions with

pruritus. The patient had been diagnosed with diabetes mellitus at age 30 years and ITP at age 70 years. His spleen had been removed to manage the ITP at 70 years of age. Physical examination revealed multiple erythemas, vesicles, tense bullae and erosions over his entire body (Fig. 1a) and erosive lesions in his oral cavity (Fig. 1b).

Laboratory examination revealed a low level of haemoglobin (11.0 g/dl; normal 13.0–17.0 g/dl), increased white blood cell count (14,300/ μ l; normal 3,900–9,300/ μ l) (eosinophils, 14.8%; normal 0.2–4.1%; neutrophils, 61.2%; normal 38–77%), normal numbers of platelets (320,000/ μ l; normal 167,000–362,000/ μ l), and elevated levels of C-reacted protein (2.197 mg/dl; normal 0.3 mg/dl or lower), haemoglobin A1c (HbA1c, 6.8%; normal 4.6–6.2%), serum urea nitrogen (65 mg/dl; normal 8–20 mg/dl) and creatinine (3.23 mg/dl; normal 0.7–1.3 mg/dl). Enzyme-

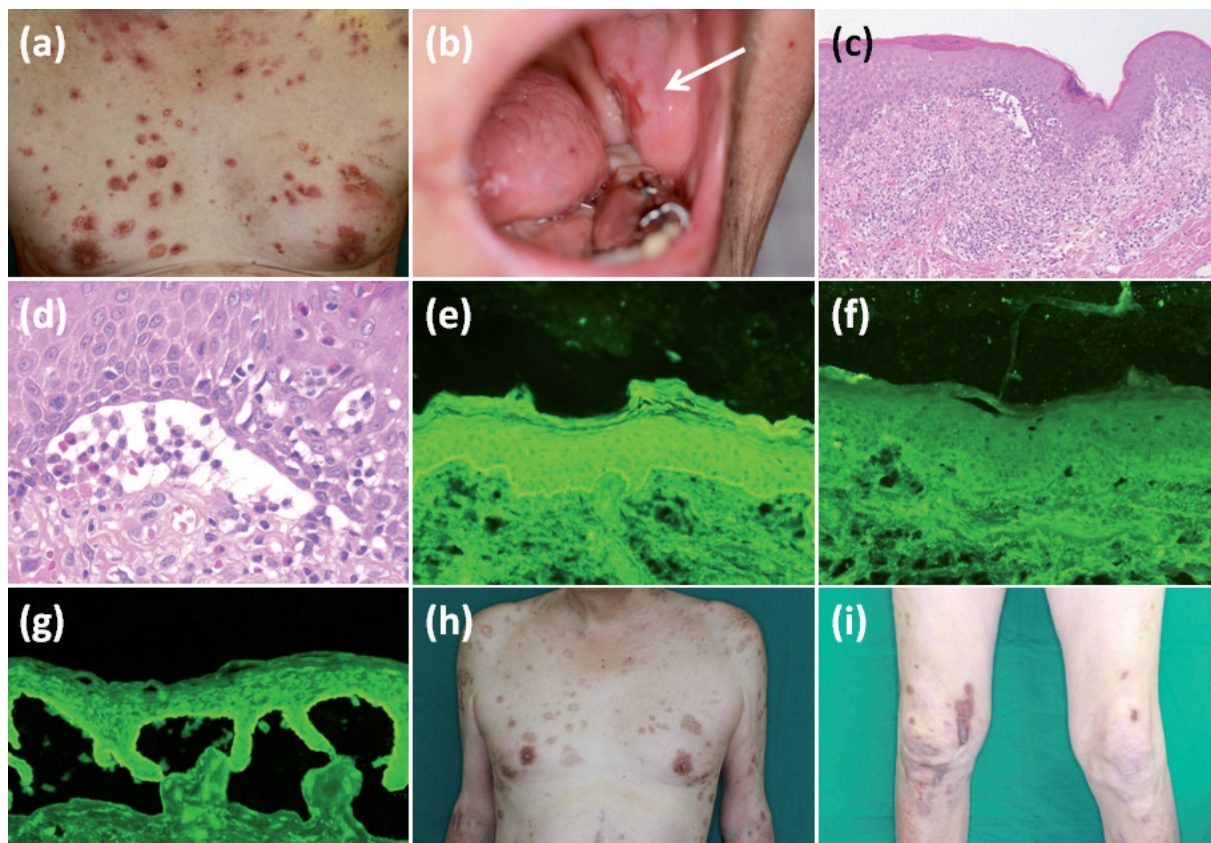


Fig. 1. Clinical and histopathological features and immunofluorescence (IF) results. (a) Skin lesion on the chest. (b) Erosive lesions in the oral cavity (arrow). (c, d) Histopathological features (haematoxylin and eosin stain, original magnifications: (c) \times 100 and (d) \times 400). (e, f) Indirect IF of normal human skin for (e) immunoglobulin (Ig)G and (f) IgA antibodies (1:40 dilution). (g) Indirect IF of 1M NaCl-split normal human skin for IgG antibodies (1:40 dilution). (h, i) Recovered skin lesions on (h) the chest and (i) the knees.

linked immunosorbent assays (ELISAs) using recombinant proteins (RPs) of desmoglein 1 (Dsg1), Dsg3, BP180 NC16a domain, and BP230 showed no positive results.

Histopathology of a skin biopsy revealed spongiosis with eosinophils and lymphocytes in the epidermis and subepidermal vacuolar change with infiltration of eosinophils and mononuclear cells in the upper dermis (Fig. 1c, d). Direct immunofluorescence (IF) showed linear deposits of IgG and C3, but not IgA, in the basement membrane zone (BMZ).

Indirect IF of normal human skin detected circulating IgG, but not IgA, anti-BMZ autoantibodies at a titre of 1:40 (Fig. 1e, f), which reacted with the epidermal side of 1M NaCl-split normal human skin (Fig. 1g). In immunoblotting of normal human epidermal extract, the patient IgG antibodies reacted weakly with BP180 (Fig. S1a¹). However, the patient sera did not react with RP of either BP180 NC16a domain or BP180 C-terminal domain. Immunoblotting of concentrated culture supernatant of HaCaT cells demonstrated clear reactivity with LAD-1 (Fig. S1b¹). Immunoblotting of normal human dermal extract and purified human laminin-332 showed no positive reactivity.

A diagnosis of MMP with IgG autoantibodies to LAD-1 was made. Oral prednisolone 40 mg/day, was started and subsequently reduced to 30 mg/day. This therapy suppressed the development of new lesions, but did not induce re-epithelization. Thus, the patient underwent intravenous immunoglobulin, 400 mg/kg/day, for 5 consecutive days with prednisolone 40 mg/day. This treatment was effective and led to re-epithelization with slight scarring (Fig. 1h, i), and oral prednisolone was subsequently tapered.

DISCUSSION

In the study of immunoblotting of human epidermal extract by Oyama et al. (4), 93 (75%) of 124 MMP patients had IgG autoantibodies to at least 1 of the BP180-related antigens (full-length BP180, LAD-1, and/or LABD97) with 14 (11.3%) patients reactive only with LAD-1. Fairley et al. (5) reported that 4 (7.8%) of 51 bullous pemphigoid (BP) sera showed negative results in an ELISA of RP of BP180 NC16a domain, and the 4 sera reacted with epitopes within the LAD-1 region by immunoblotting. In addition, several BP and MMP patients were reported to react with LAD-1, but not with NC16a or C-terminal domains of BP180 (6–9). Some of the LAD-1 reactive patients had residual scarring (5), or pruritus during the recovery stage (8). Thus, patients with IgG autoantibodies to LAD-1 seem to show clinical diversity and overlap between

BP and MMP, which is consistent with the findings in our MMP patient. We need to address what determines the development of BP or MMP.

Interestingly, 3 of 4 patients reported by Fairley et al. (5) had other autoimmune disorders; i.e., Graves disease, rheumatoid arthritis and psoriasis. Our case would be the first reported case of MMP associated with ITP. Further research is needed to determine whether BP and MMP patients with IgG anti-LAD-1 autoantibodies are predisposed to other autoimmune disorders.

The authors declare no conflicts of interest.

REFERENCES

1. Daito J, Katoh N, Asai J, Ueda E, Takenaka H, Ishii N, et al. Brunsting-Perry cicatricial pemphigoid associated with autoantibodies to the C-terminal domain of BP180. *Br J Dermatol* 2008; 159: 984–986.
2. Kurashige Y, Minemura T, Nagatani T, Koga H, Hashimoto T. Acute blistering disease presenting IgG autoantibodies against NC16A and COOH-terminal domains of BP180 and laminin-332, with characteristic distribution of eruptions. *Eur J Dermatol* 2013; 23: 109–110.
3. Aoki N, Nakajima K, Shiga T, Koga H, Hashimoto T, Sano S. A case of anti-BP180 type mucous membrane pemphigoid treated with intravenous immunoglobulin. *J Dermatol* 2014; 41: 557–559.
4. Oyama N, Setterfield JF, Powell AM, Sakuma-Oyama Y, Albert S, Bhogal BS, et al. Bullous pemphigoid antigen II (BP180) and its soluble extracellular domains are major autoantigens in mucous membrane pemphigoid: the pathogenic relevance to HLA class II alleles and disease severity. *Br J Dermatol* 2006; 154: 90–98.
5. Fairley JA, Bream M, Fullenkamp C, Syrbu S, Chen M, Messingham KN. Missing the target: characterization of bullous pemphigoid patients who are negative using the BP180 enzyme-linked immunosorbent assay. *J Am Acad Dermatol* 2013; 68: 395–403.
6. Matsui K, Makino T, Takegami Y, Murayama S, Seki Y, Ishii N, et al. Bullous pemphigoid with IgG anti-LAD-1 antibodies. *Eur J Dermatol* 2014; 24: 275–276.
7. Mariotti F, Grosso F, Terracina M, Ruffelli M, Cordiali-Fei P, Sera F, et al. Development of a novel ELISA system for detection of anti-BP180 IgG and characterization of autoantibody profile in bullous pemphigoid patients. *Br J Dermatol* 2004; 151: 1004–1010.
8. Tsuruta D, Nishikawa T, Yamagami J, Hashimoto T. Unilateral bullous pemphigoid without erythema and eosinophil infiltration in a hemiplegic patient. *J Dermatol* 2012; 39: 787–789.
9. Choi Y, Lee SE, Fukuda S, Hashimoto T, Kim SC. Mucous membrane pemphigoid with immunoglobulin G autoantibodies against full-length and 120-kDa ectodomain of BP180. *J Dermatol* 2011; 38: 169–172.

¹<https://doi.org/10.2340/00015555-1964>