Received: 4 December 2017 | Accepted: 11 January 2018

DOI: 10.1002/cia2.12000

ORIGINAL ARTICLE

WILEY Journal of Cutaneous Immunology and Allergy

Dyshidrosiform palmoplantar pemphigoid with low-titer autoantibodies against BP180 NC16A

Shinsuke Nakazawa MD[1,2] | Kentaro Izumi MD, PhD[3] | Wataru Nishie MD, PhD[3] | Hiroshi Shimizu MD, PhD[3] | Yoshiki Tokura MD, PhD[1]

[1]Department of Dermatology, Hamamatsu University School of Medicine, Hamamatsu, Japan

[2]Division of Dermatology, Morimachi Public Hospital, Morimachi, Japan

[3]Department of Dermatology, Hokkaido University Graduate School of Medicine, Sapporo, Japan

Correspondence
Shinsuke Nakazawa, Departments of Dermatology, Hamamatsu University School of Medicine, Hamamatsu, Japan.
Email: snakazawa-sin@umin.org

Abstract

Dyshidrosiform pemphigoid (DP) is a variant of bullous pemphigoid, presenting with a bullous or vesicular eruption localized on the soles and palms, and thus, DP has clinical resemblance with dyshidrosiform dermatitis. Here, we report a case of DP with literature review, focusing on the titer of antibodies directing the NC16A domain and other regions on BP180. Our case had a low titer of anti-BP180 NC16A antibodies, and our survey of literature disclosed that 10 of 20 cases of DP had low titers (index: <150, or <87.5 U/mL) of anti-BP180 NC16A antibodies. It is an issue whether DP is caused merely by a low titer of anti-BP180 NC16A antibodies or by BP-autoantibodies targeting other regions of BP180. We therefore examined our case with full-length BP180 ELISA and found the absence of such antibodies. Our study suggests that DP is associated with low-titer anti-NC16A antibodies but not with the presence of antibodies against other parts of BP180.

KEYWORDS

anti-BP180 NC16A antibodies, autoimmune bullous diseases, dyshidrosiform pemphigoid, full-length BP180 antibodies

1 | INTRODUCTION

Dyshidrosiform pemphigoid (DP), first described by Levine et al[1] is an unusual variant of bullous pemphigoid (BP), presenting with a bullous eruption localized on the soles and palms. Thus, a differential diagnosis of DP is necessary in patients with dyshidrosiform dermatitis. Because this condition is rarely reported, the presence or absence of autoantibodies to BP180 and their titer remain elusive. In addition, it is an issue whether the patients have not only autoantibodies against BP180 extracellular noncollagenous 16A domain (NC16A) but also antibodies to other regions of BP180. The latter antibodies are detectable with full-length BP180 enzyme-linked immunosorbent assay (ELISA).[2] Here, we describe a case of DP with measurements of anti-BP180 NC16A antibodies and full-length BP180 antibodies. Our review of the literature also provides information on the titer of anti-NC16A antibodies.

2 | CASE REPORT

A 74-year-old woman had suffered from a recurrent, itchy, erythematous eruption over the whole body. She was first diagnosed as having autosensitization dermatitis by another dermatologist and was treated with topical corticosteroids and oral betamethasone/d-chlorpheniramine maleate for about 10 years. She received no other medication and had no history of the central nervous system disorder. When the patient had lumbar herpes zoster and discontinued the oral medicine, severely itchy erythema occurred on her soles

and palms. She was referred to us for further evaluation of the exacerbated eruption.

On examination, the patient had an erythematous eruption on the palms (Figure 1A) and soles (Figure 1B) with multiple vesiculobullae (Figure 1C). Fungi were not detected in a specimen from vesicles. In addition to the palmoplantar lesions, edematous erythema and scratch marks were observed on the abdomen (Figure 1D) and the legs. Nikolsky's sign was negative, and the mucous membranes were normal. Blood examination showed eosinophilia (15.6%; 1,076/μL). A biopsy specimen taken from the lower leg exhibited a dermal inflammatory infiltrate composed of lymphocytes and eosinophils (Figure 1E). Direct immunofluorescence (DIF) was positive for continuous linear deposition of C3 at the dermo-epidermal junction (Figure 1F). Deposition of IgG, IgA, or IgM was not detected.

A chemiluminescent enzyme immunoassay (CLEIA) for anti-BP180 NC16A antibodies was positive, but its titer was as low as 30.9 U/mL (normal value: <9 U/mL). Measurement of enzyme-linked immunosorbent assay (ELISA) for antibodies against full-length BP180[2] was negative with index 3.20 (cutoff: <4.64). Based on these clinical and laboratory findings, a diagnosis of DP was made. The patient was treated with topical corticosteroids, oral minocycline at 200 mg daily, nicotinic acid at 900 mg daily, and levocetirizine hydrochloride at 10 mg daily, without therapeutic effects. Additional prednisone at 20 mg daily was therapeutically effective and produced a complete clinical remission.

3 | DISCUSSION

The pathogenesis of localized pemphigoid is unknown. It has been suggested that mechanical stress initiates the development of DP[3,4] and that metal allergy possibly contributes to DP.[5,6] A majority of

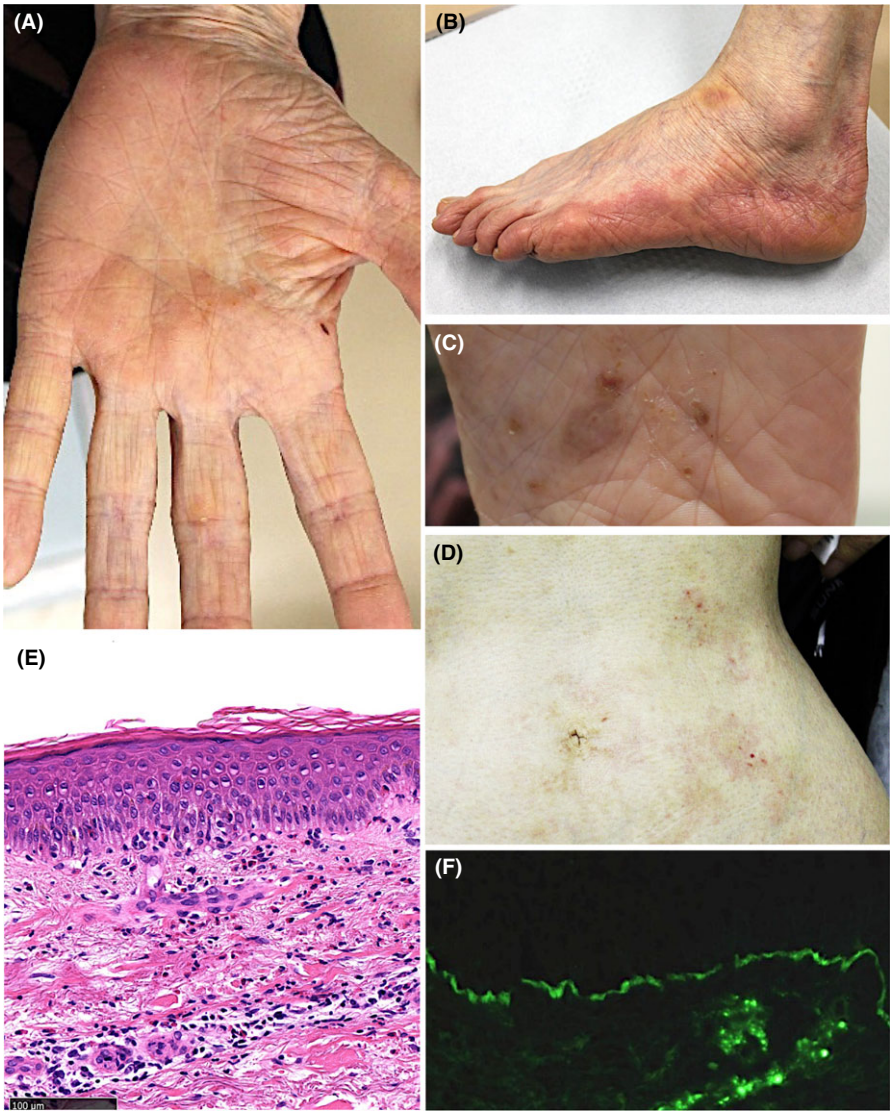

FIGURE 1 Clinical appearance and histopathological findings. Clinical photographs of erythematous lesions on the left palm (A) and left foot (B). Vesicles are observed on the plantar arch (C). Scaly erythema and crusty erythema are seen on the abdomen (D). Histology of erythematous lesion, showing infiltration of lymphocytes and eosinophils in the upper dermis with mild cleft under the epidermis (hematoxylin and eosin) (E). DIF, showing deposition of C3 (F)

TABLE 1 Reported cases of DP with anti-BP180 antibody titer

Reference	Age	Sex	Disease duration	Extrapalmoplantar eruptions	Central nervous disease	Eosinophils (%)	Anti-BP180 NC16A antibody	Direct immunofluorescence	
								IgG	C3
Konno et al[7]	85	M	3 d	–	–	42	ELISA index 125	+	+
Sugimura et al[8]	73	F	2 mo	+	–	n.d.	ELISA index 841	n.d.	+
Ishiguro et al[9]	48	F	1 y	+	–	22	ELISA index 87.2	n.d.	+
Sarayama et al[10]	74	F	1 mo	–	–	Normal	ELISA index 32.1	n.d.	+
Sato et al[11]	47	F	2 mo	+	–	25	ELISA index 103.6	+	+
Seike et al[12]	88	M	4 mo	+	–	n.d.	ELISA index 320	+	+
Ohashi et al[13]	62	M	5 y	+	–	35	ELISA index 320	+	+
Lupi et al[14]	20	M	24 mo	–	–	16.6	CLEIA 50.7 U/mL	+	+
Iijima et al[15]	57	M	3 mo	+	–	13.5	CLEIA 190.14 U/mL	+	+
Yamada et al[16]	85	M	1 mo	+	–	8	ELISA index >150	+	+
Onita et al[17]	35	F	1 mo	+	–	19.3	ELISA index >150	n.d.	+
Miyazaki et al[18]	87	M	1 mo	+	–	16	ELISA index 74	+	+
Uehara et al[19]	79	M	1 mo	+	–	37.9	CLEIA 646 U/mL	–	+
Tokunaga et al[20]	55	M	10 d	+	–	15.6	CLEIA 880 U/mL	–	+
Saito et al[21]	55	M	1 mo	–	–	8.9	CLEIA 620 U/mL	+	+
Kobayashi et al[22]	64	M	1 mo	–	Meningioma	27.8	CLEIA 84 U/mL	+	+
Matsuoka et al[23]	84	M	Some years	+	–	11	CLEIA 77.2 U/mL	n.d.	+
	78	M	6 mo	–	–	n.d.	CLEIA 142 U/mL	n.d.	n.d.
Yamaguchi et al[24]	67	M	15 mo	+	–	14	CLEIA 50.4 U/mL	n.d.	+
Our case	74	F	7 d	+	–	15.6	CLEIA 30.9 U/mL	–	+

n.d., not done.

autoantibodies for BP target the juxtamembranous NC16A domain of BP180.[2] We surveyed cases of DP reported in 2003-2017 and selected the cases that were clearly documented with anti-BP180 NC16a antibody titers (Table 1). In addition to eruptions on the palms and soles, extrapalmoplantar lesions were observed in 14 of 20 cases as seen in our patient. Peripheral blood eosinophilia was seen in 14 of 17 cases as seen in usual BP. DIF showed C3 deposition in all cases (19 of 19 cases) and IgG deposition in 10 of 13 cases. Notably, differing from usual BP, low titers (index < 150, or <87.5 U/mL) of anti-BP180 NC16A antibody were found in 10 of 20 cases. The high-titer group has extrapalmoplantar eruptions at a high frequency (8 of 10 cases). On the other hand, there is no relationship between the titer and the disease duration.

Bullous pemphigoid autoantibodies may target other regions of BP180 than the NC16A domain. Recently, Izumi et al[2] established full-length BP180 ELISA. Considering that the anti-NC16A titer was low, it was found possible that autoantibodies against the regions other than the NC16A domain were present in DP cases. However, the full-length BP180 ELISA negated this possibility in our case. It is unclear why BP-autoantibodies exclusively target NC16A but not full-length BP180. The possible reason may relate to the sensitivity. Alternatively, the generation of neoepitopes within NC16A after the cleavage of the BP180 ectodomain may be involved.[2]

Our study suggests that DP is associated with low-titer anti-NC16A antibodies but not with the presence of antibodies against other parts of BP180. It remains elusive in our study why the low-titer antibodies preferentially induce palmoplantar lesions. Future studies are required to address the question of whether these predilection sites are prone to receive some mechanical stimuli or whether other elements are involved in the disease occurrence.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

Shinsuke Nakazawa http://orcid.org/0000-0003-3553-796X

REFERENCES

1. Levine N, Abraham F, Barland P. Localized pemphigoid simulating dyshidrosiform dermatitis. Arch Dermatol. 1979;115:320–1.
2. Izumi K, Nishie W, Mai Y, et al. Autoantibody profile differentiates between inflammatory and noninflammatory bullous pemphigoid. J Invest Dermatol. 2016;136:2201–10.

3. Forschner A, Fierlbeck G. Localized pemphigoid on the soles of both feet. Int J Dermatol. 2005;44:312–4.
4. Kobayashi Y, Harada K, Abe N, Tsuboi R, Oshima Y, Mihashi Y. Dyshidrosiform pemphigoid. Pract Dermatol 2014;36:737–40 (Japanese).
5. Sarayama Y, Shimizu H, Adachi A. A case of dyshidrosiform pemphigoid, treatment with Nickel free diet. Japanese J Clin Dermatol 2005;47:852–6 (Japanese).
6. Atakan N, Tüzün J, Karaduman A. Dyshidrosiform pemphigoid induced by nickel in the diet. Contact Dermatitis. 1993;29:159–60.
7. Konno T, Ishizawa T, Mitsuhashi Y. Dyshidrosiform pemphigoid. Pract Dermatol. 2003;26:55–8 (Japanese).
8. Sugimura C, Katsuura J, Moriue T, Matsuoka Y, Kubota Y. Dyshidrosiform Pemphigoid: Report of a Case. J Dermatol. 2003;30:525–9.
9. Ishiguro H, Nakajima H, Ikeda M, Kodama H. A case of dyshidrosiform pemphigoid. Rinsho Derma. 2004;46:1849–52 (Japanese).
10. Sarayama Y, Shimizu H, Adachi A. A case of dyshidrosiform pemphigoid. Rinsho Derma. 2005;47:852–856 (Japanese).
11. Sato T, Maruyama H, Ito S, Takahashi T, Kawachi Y, Otsuka F. A case of dyshidrosiform pemphigoi d. Rinsho Derma. 2006;48:1119–22 (Japanese).
12. Seike M, Nakajima K, Ikeda M, Kodama H. Coexistence of nodular and dyshidrosiform pemphigoid. J Dermatol. 2006;33:375–6.
13. Ohashi S, Arai R, Masatsugu A, Ohta M, Horiguchi Y. A case of bullous pemphigoid showing like autosensitization dermatitis. Skin Research. 2009;8:164–7 (Japanese).
14. Lupi F, Masini C, Ruffelli M, Puddu P, Cianchini G. Dyshidrosiform palmoplantar pemphigoid in a young man: response to dapsone. Acta Derm Venereol. 2010;90:80–1.
15. Iijima S, Sato T, Ebihara I, Hashimoto T. A case of bullous pemphigoid: response to DFPP. Rinse Derma. 2010;52:659–64 (Japanese).
16. Yamada Y, Sugita K, Izu K, Nakamura M, Tokura Y. A case of dyshidrosiform pemphigoid. J UOEH. 2011;33:183–7 (Japanese).
17. Onita A, Okubo Y, Naitou S, Ichinomiya A. A case of bullous pemphigoid starting from palmoplantar vesicles. Pract Dermatol. 2012;34:469–72 (Japanese).
18. Miyazaki R, Ohtsuka T, Katagiri K. A case of dyshidrosiform pemphigoid. Pract Dermatol. 2012;34:155–8 (Japanese).
19. Uehara A, Yamada K, Hasegawa M, Nagai Y, Tamura A, Ishikawa O. A case of dyshidrosiform pemphigoid with anti desmoglein 1. Rinsho Derma. 2012;54:87–90 (Japanese).
20. Tokunaga M, Endo Y, Nakahigashi K, et al. A case of bullous pemphigoid showing like dyshidrosis. Rinse Derma. 2013;55:842–3 (Japanese).
21. Saito M, Kimura U, Kinoshita A, Suga Y. Dyshidrosiform pemphigoid. Pract Dermatol. 2014;36:733–6 (Japanese).
22. Kobayashi Y, Harada K, Abe N, Tsuboi R, Oshima Y, Mitsuhashi Y. Dyshidrosiform pemphigoid. Pract Dermatol. 2012;34:73–40 (Japanese).
23. Matsuoka Y, Ansai S, Ogita A, et al. Two cases of pemphigoid nodularis with dyshidorosis. Rinse Derma. 2016;58:1533–6 (Japanese).
24. Yamaguchi H, Aoshima M, Fukuchi K, Hoshino T, Tokura Y. A case of dyshidrosiform pemphigoid. Rinsho Derma. 2016;58:24–5 (Japanese).

How to cite this article: Nakazawa S, Izumi K, Nishie W, Shimizu H, Tokura Y. Dyshidrosiform palmoplantar pemphigoid with low-titer autoantibodies against BP180 NC16A. *J Cutan Immunol Allergy*. 2018;1:27–30. https://doi.org/10.1002/cia2.12000