Received: 21 September 2020 | Revised: 19 January 2021 | Accepted: 20 January 2021

DOI: 10.1002/cia2.12162

Journal of Cutaneous Immunology and Allergy

WILEY

CORRESPONDENCE

Bullous pemphigoid receiving a novel long-acting dipeptidyl-peptidase-4 (DPP-4) inhibitor omarigliptin in a patient with type 2 diabetes: A case report

Dear Editor,

Drug-induced bullous pemphigoid (BP) has added to an increasing association with dipeptidyl-peptidase-4 inhibitors (DPP4i). Among various DPP4i used for the treatment of diabetes, omarigliptin is an once-weekly oral agent that received the first global approval in Japan and widely used in anti-diabetic algorithm; however, reports only implicate a potential risk for developing BP comparable with other DPP4i.[1] We report, to our knowledge, the first case of BP receiving omarigliptin, whose serum IgG targets BP180-NC16a.

A 65-year-old Japanese man presented a 6-month history of itchy blisters on the face and trunk. Combined with preceded mitiglinide calcium hydrate voglibose, he had received once-weekly DPP4i omarigliptin for diabetes 30 months before. Examination showed fingertip-sized tense blisters and erosions on his face and back (Figure 1A, B).

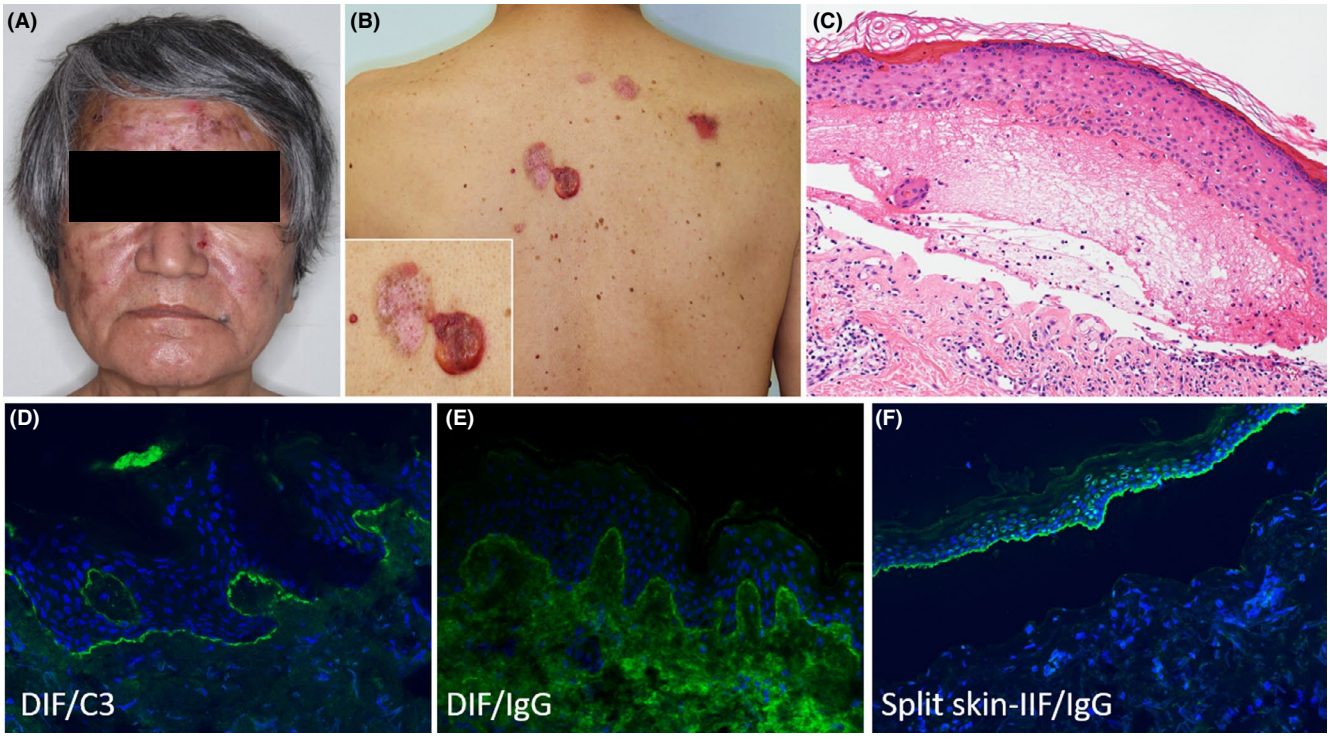

FIGURE 1 (A) Flaccid blisters and erosions with crusts of less than 1 cm in diameter on the face. (B) Fingertip-sized blisters and erosions on the upper back. *Inset* indicates the higher magnification. (C) Histopathology showing subepidermal blister formation with eosinophils and lymphocyte infiltration in the upper dermis (HE x100). (D-E) Direct immunofluorescence showing linear C3 (D) and IgG deposits (E) at the basement membrane zone. (F) 1M NaCl-split skin indirect immunofluorescence showing positive IgG staining at the roof side of the basement membrane zone

There was no obvious erythema and mucous lesions. Laboratory workup revealed no abnormality. Chemiluminescent enzyme immunoassay was positive for BP180-NC16a IgG (74.8 U/mL; normal < 9.0 U/mL) but was negative for BP230 IgG. Histopathology showed subepidermal blister with eosinophil and lymphocyte infiltration in the upper dermis (Figure 1C). Direct immunofluorescence showed linear deposits of C3 and IgG along dermal-epidermal junction (Figure 1D, E). 1M NaCl-split skin indirect immunofluorescence showed positive IgG staining at the roof basement membrane zone (Figure 1F). These findings suggest a diagnosis of BP probably associated with omarigliptin. BP Disease Area Index was total 8 (8-0-0). Omarigliptin intake was withdrawn, and a topical steroid therapy with clobetasol propionate 0.05% was initiated. His skin lesions were soothed thereafter, although serum anti-BP180-NC16a antibody titer remained fluctuated at the high level (74.8-101.6 U/mL).

Meta-analysis of observational studies and randomized control trials explored a close association of DPP4i in developing BP, with 2- to 4-fold increased risk.[2,3] However, no substantial reports are available regarding the cause of once-weekly, long-acting DPP4i, omarigliptin or trelagliptin, in BP, except one Japanese case.[1] The poor evidence would be due to the limited marketing that the two DPP4i are approved only in Japan.

Our case had a discrepancy between the clinical activity and antibody titer. This may implicate the presence of pathogenic autoantibodies targeting epitopes, other than BP180-NC16a, as heterogeneous autoantibody profile to hemidesmosomal antigens has been demonstrable in DPP4i-associated BP.[4–6] Of these, however, the pathogenic significance of autoimmunity to full-length BP180 remains inconclusive, because diabetic patients with DPP4i carry a high occurrence of serum anti-full-length BP180 antibody even without mucocutaneous manifestation (10.9%),[7] and in diabetic cohort with DPP4i, all the BP patients with anti-BP180-NC16a antibody (n = 13) also had positive IgG for full-length antigen.[4] Our case might therefore share anti-full-length BP180 antibody, although the further serological screening was postponed. Another possibility may simply raise the coincidence of BP and occasional administration of omarigliptin. Considering that diabetic condition per se increases the risk of BP,[8] medical background including other anti-diabetic drugs might cooperatively modify the antigenicity of target antigen(s) and/or immunoglobulin subtypes,[9] as well as baseline activity of the disease. Because of the unique pharmacokinetics of omarigliptin with low IC50 value (~1.6 nmol/L),[10] our case may alert prolonged adverse skin events after withdrawal of suspected DPP4i.

KEYWORDS

anti-BP180-NC16a autoantibody, autoimmune bullous disease, bullous pemphigoid, dipeptidyl-peptidase-4 inhibitor, omarigliptin

CONFLICT OF INTEREST

The author declared no conflict of interest.

DECLARATION SECTION

Approval of the research protocol: No human participants were included.

Informed Consent: Obtained.

Registry and the Registration No.: N/A.

Animal Studies: N/A.

Hiroshi Kasamatsu MD[1,2]
Takenao Chino MD, PhD[2]
Noritaka Oyama MD, PhD[2]
Takakiyo Nakaya MD[3]
Minoru Hasegawa MD, PhD[2]

[1]*Department of Dermatology, Tannan Regional Medical Center, Fukui, Japan*
[2]*Department of Dermatology, Faculty of Medical Sciences, University of Fukui, Fukui, Japan*
[3]*Department of Internal Medicine, Tannan Regional Medical Center, Fukui, Japan*

Correspondence
Hiroshi Kasamatsu MD, Department of Dermatology, Faculty of Medical Sciences, University of Fukui, 23-3 Matsuoka-Shimoaizuki, Eiheiji-cho, Yoshida-gun, Fukui 910-1193, Japan.
Email: handm830@u-fukui.ac.jp

ORCID

Hiroshi Kasamatsu https://orcid.org/0000-0002-2224-9507
Takenao Chino https://orcid.org/0000-0002-2224-3383
Noritaka Oyama https://orcid.org/0000-0003-4934-5205
Minoru Hasegawa https://orcid.org/0000-0003-3738-2682

REFERENCES

1. Mai Y, Nishie W, Izumi K, Shimizu H. Preferential reactivity of Dipeptidyl Peptidase-IV inhibitor-associated bullous pemphigoid autoantibodies to the processed extracellular domains of BP180. Front Immunol. 2019;10:1224.
2. Kridin K, Cohen AD. Dipeptidyl-peptidase IV inhibitor-associated bullous pemphigoid: A systematic review and meta-analysis. J Am Acad Dermatol. 2018. https://doi.org/10.1016/j.jaad.2018.09.048. Online ahead of print.
3. Varpuluoma O, Försti AK, Jokelainen J, Turpeinen M, Timonen M, Huilaja L, et al. Vildagliptin significantly increases the risk of Bullous Pemphigoid: A finnish nationwide registry study. J Invest Dermatol. 2018;138:1659–61.
4. Izumi K, Nishie W, Mai Y, Wada M, Natsuga K, Ujiie H, et al. Autoantibody profile differentiates between inflammatory and noninflammatory Bullous Pemphigoid. J Invest Dermatol. 2016;136:2201–10.
5. Fania L, Salemme A, Provini A, Pagnanelli G, Collina MC, Abeni D, et al. Detection and characterization of IgG, IgE, and IgA autoantibodies in patients with bullous pemphigoid associated with dipeptidyl peptidase-4 inhibitors. J Am Acad Dermatol. 2018;78:592–5.
6. Sawada K, Sawada T, Kobayashi T, Fujiki A, Matsushita T, Kawara S, et al. A case of anti-BP230 antibody-positive bullous pemphigoid receiving DPP-4 inhibitor. Immunol Med. 2020;7:1–3.
7. Izumi K, Nishie W, Beniko M, Shimizu H. A cross-sectional study comparing the prevalence of bullous pemphigoid autoantibodies in 275 Cases of Type II diabetes mellitus treated with or without Dipeptidyl Peptidase-IV inhibitors. Front Immunol. 2019;10:1439.

8. Chuang TY, Korkij W, Soltani K, Clayman J, Cook J. Increased frequency of diabetes mellitus in patients with bullous pemphigoid: a case-control study. J Am Acad Dermatol. 1984;11:1099–102.
9. Lee SG, Lee HJ, Yoon MS, Kim DH. Association of Dipeptidyl Peptidase 4 Inhibitor Use With Risk of Bullous Pemphigoid in Patients With Diabetes. JAMA Dermatol. 2019;155:172–7.
10. Biftu T, Sinha-Roy R, Chen P, Qian X, Feng D, Kuethe JT, et al. Omarigliptin (MK-3102): a novel long-acting DPP-4 inhibitor for once-weekly treatment of type 2 diabetes. J Med Chem. 2014;57:3205–12.