DOI: 10.1002/cia2.12006

WILEY Journal of Cutaneous Immunology and Allergy

LETTER TO THE EDITOR

Linagliptin treatment-associated bullous pemphigoid presenting severe mucosal erosions

Dear Editor,

It was recently reported that some cases of bullous pemphigoid (BP) were induced by dipeptidyl peptidase (DPP)-4 inhibitors used for the treatment of type 2 diabetes mellitus. We present a case of BP with severe esophageal mucosal erosions occurring during linagliptin administration.

A 64-year-old man with diabetes mellitus was referred to our department complaining of a diffuse eruption of bullae and erosions

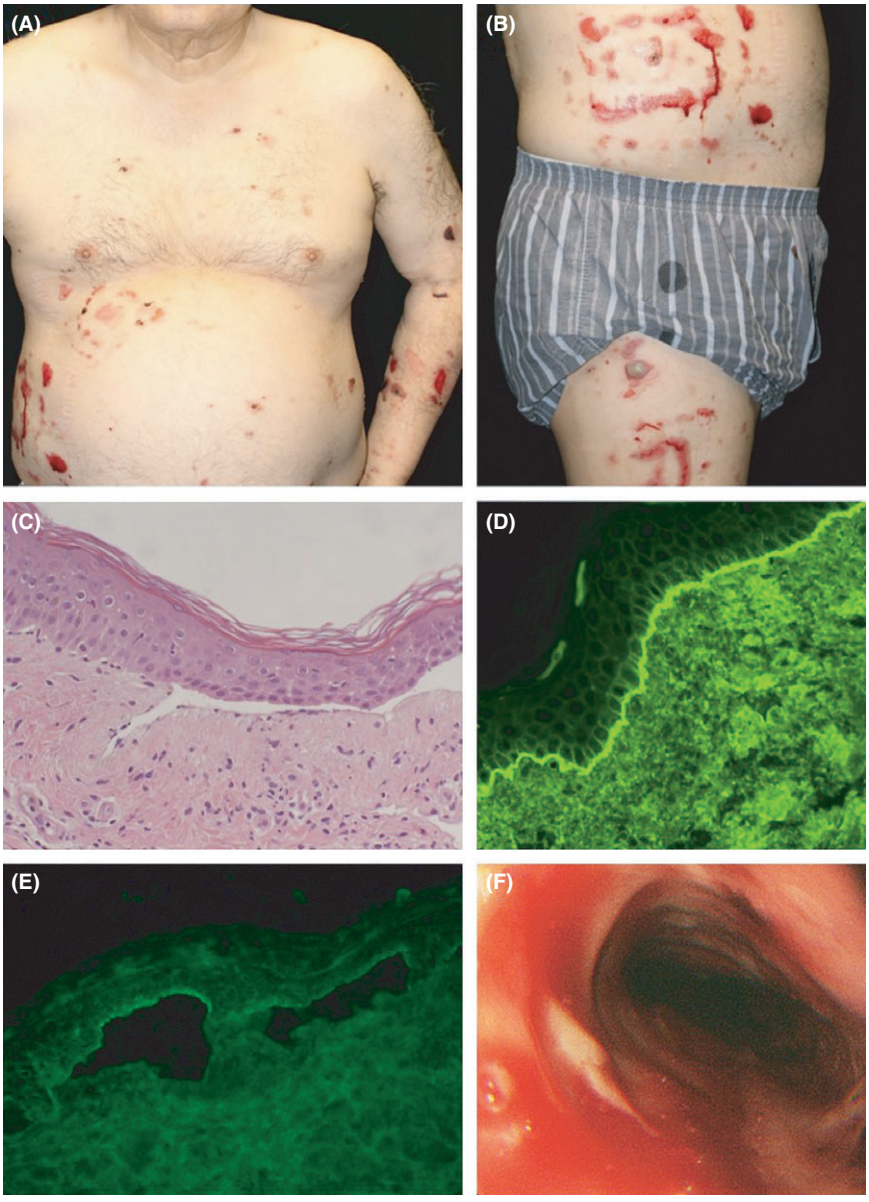

FIGURE 1 A, B, Clinical images. Erosive lesions with few erythema were seen on his trunk and limbs. C, Histopathology from the outside of the right leg revealed subepidermal blisters (hematoxylin-eosin stain, original magnification ×200). D, Direct immunofluorescence analysis revealed a linear deposition of immunoglobulin G at the basement membrane zone. A similar linear deposition of complement C3 was also detected. E, Indirect immunofluorescence microscopy on salt-split skin revealed staining to the epidermal side. F, Esophagogastroduodenoscopy showed severe hemorrhagic erosions in the esophagus

with slight erythema on his head, trunk, and limbs (Figure 1A,B). The patient also complained of oral erosive lesions. Linagliptin, which is a DPP-4 inhibitor, had been started 6 months previously. A skin biopsy revealed subepidermal blisters containing few eosinophils (Figure 1C). Direct immunofluorescence staining revealed a linear deposition of immunoglobulin G and complement C3 along the basement membrane zone (Figure 1D). A chemiluminescence enzyme immunoassay for the BP180 NC16A antibody and an enzyme-linked immunosorbent assay (ELISA) for BP230 antigen were performed, and both showed negative results. An ELISA for the detection of antibodies targeting the full-length collagen (COL) 17[1] yielded a strongly positive result (ELISA index 121.7, cutoff <4.64). Indirect immunofluorescence microscopy on salt-split skin revealed staining to the epidermal side (Figure 1E). Therefore, we ruled out the presence of antibodies targeting laminin gamma-1, laminin 332, and COL7. BP with autoantibodies targeting full-length COL17 without NC16A can occasionally develop in patients treated with DPP-4 inhibitors.[1] Taken together, the patient was diagnosed with BP with autoantibodies targeting full-length COL17, which was probably caused by the DPP-4 inhibitor.

After the withdrawal of linagliptin, the cutaneous lesions were improved in 2 weeks. However, esophagogastroduodenoscopy showed severe hemorrhagic erosions in the esophagus (Figure 1F). Therefore, 0.3 mg/kg/d oral prednisolone was started, and significant improvements of the erosions of both skin and esophagus were observed immediately. Two weeks after starting oral prednisolone, a second esophagogastroduodenoscopy showed mostly epithelialization in the esophagus. The ELISA for full-length COL17 was performed again after all the cutaneous and mucous lesions resolved and yielded a negative result.

The number of reported cases of BP induced by linagliptin has been increasing during the past few years.[2–6] A large-scale analysis of BP induced by DPP-4 inhibitors was performed using the European pharmacovigilance database.[7] According to the data, the proportional reporting ratio for linagliptin and BP was the second highest after that for vildagliptin. However, it has not previously been reported that the mucous membranes are severely affected in patients using DPP-4 inhibitors including linagliptin. In our case, the skin lesion was relieved by cancelation of the DPP-4 inhibitor, but the esophagus lesion did not cure without steroid treatment.

It was reported that BP with autoantibodies targeting full-length COL17 without NC16A clinically demonstrated noninflammatory eruptions, and histopathological findings demonstrated few eosinophils,[1] which is compatible with the symptoms and histopathology of our case. The pathogenesis and the reason why the lesions are noninflammatory or less-inflammatory are still under investigation.

In conclusion, DPP-4 inhibitors should be considered as a possible trigger of BP and also severe esophagus lesion that may be prolonged even after discontinuation of DPP-4 inhibitors.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

Junko Mukaijo http://orcid.org/0000-0001-8650-1591

Junko Mukaijo MD[1]
Miwa Kanaoka MD[1]
Katsuyuki Kawano MD[1]
Setsuko Matsukura MD, PhD[1]
Takashi Hibiya MD, PhD[2]
Akio Miyake MD[2]
Kentaro Izumi MD, PhD[3]
Wataru Nishie MD, PhD[3]
Hiroshi Shimizu MD, PhD[3]
Michiko Aihara MD, PhD[1]

[1]*Department of Dermatology, Yokohama City University School of Medicine, Yokohama, Japan*
[2]*Department of Pathology, Yokohama City University School of Medicine, Yokohama, Japan*
[3]*Department of Dermatology, Hokkaido University Graduate School of Medicine, Sapporo, Japan*

Correspondence
Junko Mukaijo, Department of Dermatology, Yokohama City University School of Medicine, Yokohama, Japan.
Email: yjunko0403@yahoo.co.jp

REFERENCES

1. Izumi K, Nishie W, Mai Y, et al. Autoantibody profile differentiates between inflammatory and noninflammatory bullous pemphigoid. J Invest Dermatol. 2016;136:2201–10.
2. Mendonca FM, Martin-Gutierres FJ, Rios-Martin JJ, Camacho-Martinez F. Three cases of bullous pemphigoid associated with dipeptidyl peptidase-4 inhibitors – one due to linagliptin. Dermatology. 2016;232:249–53.
3. Harber R, Fayad AM, Stephan F, Obeid G, Tomb R. Bullous pemphigoid associated with linagliptin treatment. JAMA Dermatol. 2016;152:224–6.
4. Sakai A, Shimomura Y, Ansai O, et al. Linagliptin-associated bullous pemphigoid that most likely caused by IgG autoantibodies against the midportion of BP180. Br J Dermatol. 2017;176:541–3.
5. Esposito I, Moretta G, Peris K, De Simone C. Linagliptin-induced bullous pemphigoid. Int J Dermatol. 2017;56:1467–9.
6. Yoshiji S, Murakami T, Harashima SI, et al. Bullous pemphigoid associated with dipeptidyl peptidase-4 inhibitors: a report of five cases. J Diabetes Investig. 2018;9:445–7. https://doi.org/10.1111/jdi.12695.
7. García M, Aranburu MA, Palacios-Zabalza I, Lertxundi U, Aguirre C. Dipeptidyl peptidase-IV inhibitors induced bullous pemphigoid: a case report and analysis of cases reported in the European pharmacovigilance database. J Clin Pharm Ther. 2016;41:368–70.