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CLINICAL LETTER

# Esophageal involvement in DPP4 inhibitor-associated bullous pemphigoid

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Dear Editors,

Dipeptidyl-peptidase 4 inhibitors (DPP4i) are widely used hypoglycemic drugs strongly associated with bullous pemphigoid (BP), the most common autoimmune subepidermal blistering disease.[1,2] DPP4i-associated BP may display differences in histological, immunological, and clinical features.[1–3] Here we present the case of a patient treated with DPP4i who developed a severe BP involving both the skin and esophagus.

A 69-year-old male with type 2 diabetes mellitus and a 2-year history of alogliptin treatment presented to the emergency room with a 2-week history of dyspnea, dysphagia and, most recently, hematemesis. He had also been under investigation for skin blisters over the prior months and received tapering doses of prednisone. Physical examination showed widespread urticarial plaques, serohemorrhagic tense blisters, and erosions (Figure 1a). Nikolsky's sign was negative. There were no mucosal lesions (Bullous Pemphigoid Disease Area Index [BPDAI] score: 83). Blood tests showed anemia (7.8 g/dl) and slight elevation of C-reactive protein. An emergent upper endoscopy showed severe mucosal detachment of both the hypopharynx and esophagus with mucosal necrotic debris occupying the lumen (Figure 2a). The stomach and duodenum were normal. Skin biopsy showed a subepidermal blister with dermal eosinophils while direct immunofluorescence examination (DIF) revealed linear IgG and C3 deposits along the BMZ with an N-serrated pattern (Figure 1b, c). Esophagus biopsies revealed separation of the epithelium and granulation tissue, and positive DIF for IgG, C3 and fibrinogen at the BMZ and in the intercellular spaces of basal keratinocytes (Figure 2b, c). Indirect immunofluorescence examination on human salt split skin demonstrated low titer (1:10) circulating IgG autoantibodies binding to the epidermal side of the BMZ. Autoantibodies against BP180 (> 200 U/ml) were also detected by NC16a-ELISA, further confirming the diagnosis of BP. The individual was admitted to the intensive care unit, requiring transfusion support and intravenous methylprednisolone (0.5 mg/kg body weight/day). After 3 weeks, there was progressive improvement in mucosal lesions and the patient exhibited milia within the resolving BP lesions. Nonetheless, upon complete resolution of the skin lesions, no scarring occurred. New endoscopies and biopsies confirmed the disappearance of histological and DIF indicators. Following medical discharge, the patient adjusted his antidiabetic treatment and alogliptin was discontinued.

Esophageal involvement in BP is rare and only a few cases have been reported. Its clinical manifestations are often nonspecific such as dysphagia and upper gastrointestinal bleeding. While mucosal involvement is frequent in pemphigus and has been correlated with the type of antibodies detected, the pathogenesis of mucosal involve-

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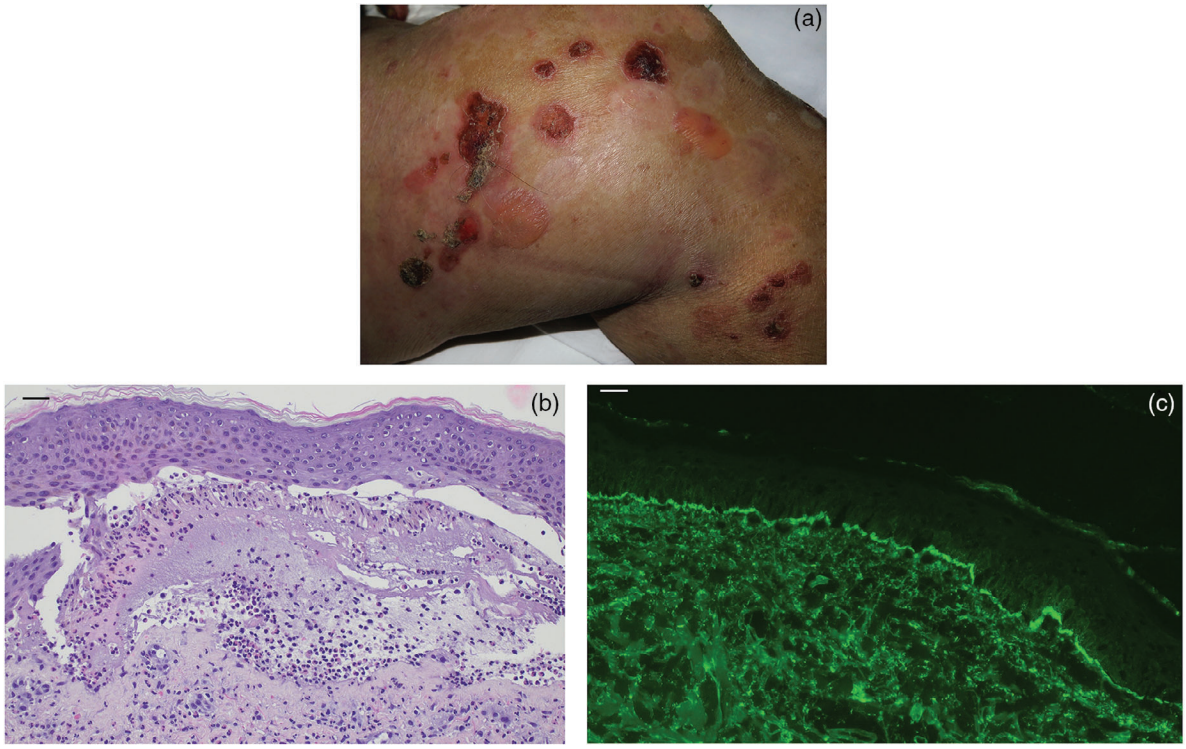


**FIGURE 1** (a) Tense blisters and erosions over urticarial plaques on the thighs. (b) Subepithelial blister with abundant eosinophils in the dermis (hematoxylin-eosin). (c) Direct immunofluorescence showing linear IgG deposition along the basement membrane zone with an n-serrated pattern (scale bar: (b) 50 $\mu$m, (c) 50 $\mu$m).

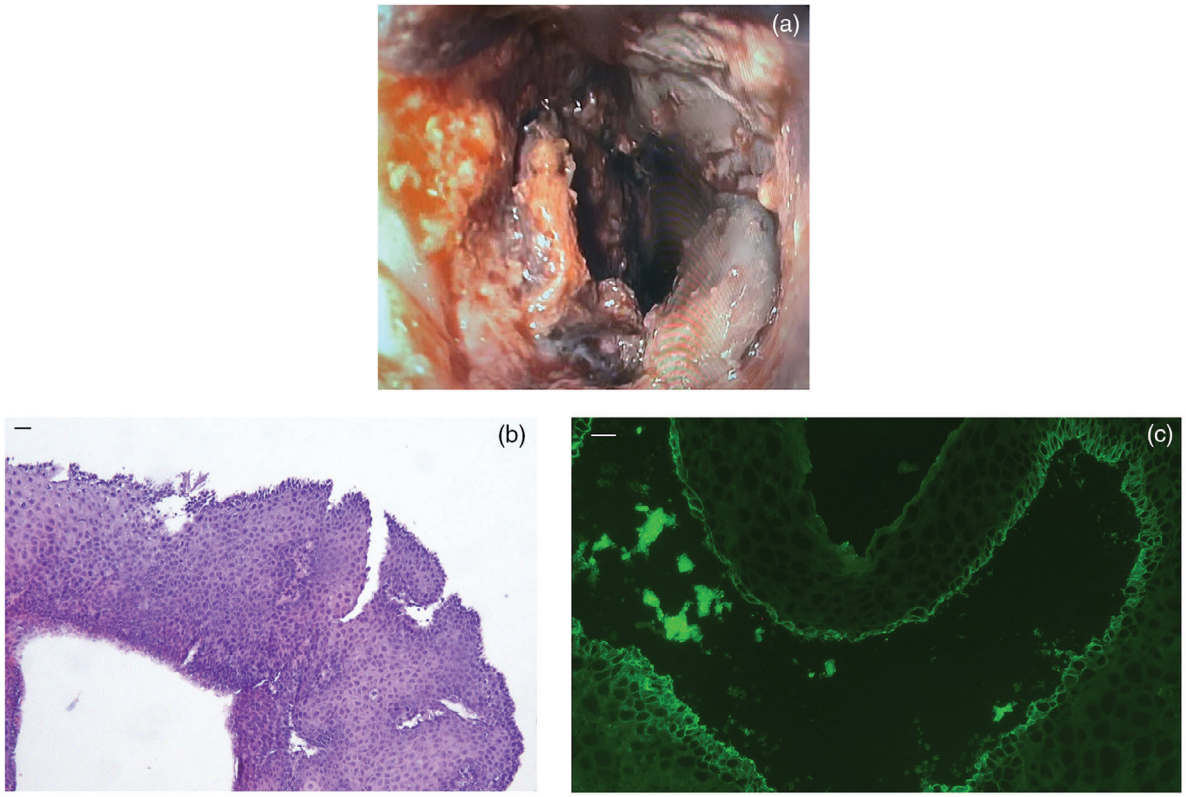


**FIGURE 2** (a) Esophageal involvement. Proximal third of esophagus showing severe mucosal inflammation, friability and bleeding with mucosal detachment and debris occupying the lumen. (b) Granulation tissue and surface fragments of squamous epithelium with mild basal hyperplasia (hematoxylin-eosin). (c) Direct immunofluorescence showing IgG deposits at the basement membrane zone, as well as in the intercellular spaces of basal keratinocytes. (scale bar: (b) 25 $\mu$m, (c) bar 50 $\mu$m).

ment in BP is poorly understood.[4] It has been suggested that tissue damage may reveal mucosal tissue-specific antigens that generate pathogenic antibodies.[4] Various drugs, including antibiotics, diuretics, TNF$\alpha$ inhibitors, and recently, anti-PD/PD-L1, and DPP4i have been associated with BP.[6] Interestingly, our case prompts a discussion on the distinctions between mucous membrane pemphigoid (MMP) and BP. Mucous membrane pemphigoid usually involves the oral mucosa from the outset. Moreover, esophageal involvement, if present, tend to appear years after disease onset. Additionally, the eventual skin involvement in MMP follows mucosal lesions with a head and neck predominance and a tendency to heal with scarring.[7,8]

Our patient developed BP after nearly 2 years of gliptin treatment, which is longer than the mean time reported.[1] DPP4i-associated BP may express more severe phenotypes, with greater mucosal involvement, such as in the conjunctiva and the oral cavity.[1,9] However, our patient did not present lesions in the oral cavity, a situation also reported in non-DPP4i-associated BP involving the esophagus.[5,10] Additionally, our case was associated with alogliptin, although the most severe cases of DPP4i-associated BP have been related with vildagliptin and linagliptin.[1,2,11]

The endoscopic findings were similar to those found in non-DPP4i-associated BP, with friable mucosa and necrotic and hemorrhagic areas, leading to esophagitis dissecans superficialis.[10] The observation in our case of IgG deposits on the intercellular spaces of esophageal basal keratinocytes, in addition to BMZ, may be explained by a relocation of hemidesmosomal antigens due to the inflammatory process. Treatment usually involves systemic corticosteroids, and non-mechanical hemostatic methods are preferred for gastrointestinal bleeding due to mucosal friability. There is no clear evidence regarding endoscopic treatment in this condition.[5,10,13]

Esophageal involvement in BP is rare but severe and should be considered when facing patients with gastrointestinal symptoms. To our knowledge, this is the first case of DPP4i-associated BP with esophageal involvement.

## CONFLICT OF INTEREST

None.

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