Acquired Haemophilia A in DPP4 Inhibitor-induced Bullous Pemphigoid as Immune Reconstitution Syndrome

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Acquired haemophilia A (AHA) is a relatively rare disorder caused by spontaneous production of neutralizing immunoglobulin (Ig)G autoantibodies against endogenous factor VIII (FVIII), called inhibitors (1, 2). AHA is often associated with pregnancy, the post-partum period, malignancy, autoimmune diseases, infections, and certain medications (2, 3). Among these, the association with bullous pemphigoid (BP) has recently received attention. According to a recent review, BP was usually diagnosed a few months prior to AHA onset, none of the cases of AHA developed prior to the onset of BP (4, 5), and many patients with BP developed AHA during a corticosteroid taper (4). Given the frequent onset of AHA in the postpartum setting, it can be hypothesized that AHA might emerge as a manifestation of immune reconstitution inflammatory syndrome (IRIS), a condition that has been described in immunosuppressed individuals once immune function is restored (6, 7).

We report here the case of a woman who developed dipeptidyl peptidase 4 inhibitors (DPP-4is)-associated BP during and after treatment with DPP-4is and cessation of systemic corticosteroids. Although the patient initially showed positive reactivity to full-length BP180 (fBP180) domain in enzyme-linked immunosorbent assay (ELISA), and, upon treatment with systemic corticosteroids, the subsequent reactivity decreased with clinical improvement. Subsequent severe flaring of the disease occurred in association with the shift to positive reactivity with BP180 NC16a and the development of FVIII inhibitors (FVIIIis), resulting in the onset of AHA.

CASE REPORT

A 78-year-old woman presented with small, tense blisters on her face, shoulders and upper back. She was initially prescribed linagliptin followed by alogliptin benzoate for diabetes, for 2 years (**Fig. 1**a). A biopsy found subepidermal bulla formation and numerous eosinophils lining up along the dermoepidermal junction. Direct immunofluorescence revealed linear deposition of IgG and C3 along the basement membrane zone and positive reactivity of IgG with the epidermal side of 1M NaCl-split-skin and anti-fBP180 antibody in ELISA (39.6 index value), negative serum level of anti-BP180NC16a antibody (<3.0 U/ml) anti-BP230 antibody (2.4 index value) consistent with the clinical diagnosis of DPP-4is-associated BP (Fig. 1 b, c) (8). Although alogliptin was suspected, the patient did not agree with drug withdrawal. Bullous lesions completely resolved one month after starting oral prednisolone. When prednisolone was tapered to 5 mg daily, alogliptin was discontinued. Six weeks after withdrawal of prednisolone (day 215), however, bullae, erosions, or ulcerations developed in the oral mucosa, especially on the gingiva. Before the flaring of oral lesions, she had noted recurrent genital bleeding. Skin biopsy revealed subepidermal blistering with linear deposition of IgG and C3 along the basement membrane zone. Her BP recurred at mucous membrane lesions. The patient reported continuous bleeding from the biopsy site. However, the mucous erosions and bleeding resolved after re-starting prednisolone 20 mg. When prednisolone was tapered to 3 mg daily, the patient frequently experienced continuous bleeding, associated with removal of tooth and surgical procedures. Laboratory investigation showed prolongation of activated partial prothrombin time (APTT) of 55.6 s (normal range 24.0–40.0 s), but with normal prothrombin time and platelet counts. Coagulation factor assay revealed a profound decrease in FVIII levels at 3% (normal range 60–150%) and a high-titre of FVIIIis at 8.0 BU/ml (normal 0–0.6 BU/ml), normal activity of von Willebrand factor, thus confirming a diagnosis of AHA. As shown in Fig. S1[1], serum tests showed an increase in BP180NC16aAb titres after day 229, while a marked decrease in fBP-180Ab titres was noted at onset and relapse of AHA. Finally, the patient was again prescribed prednisolone, 20 mg/day, which was sufficient to control the AHA symptoms. The prednisolone dose was gradually tapered to a maintenance dose of 10 mg/day with no subsequent bleeding episodes or blisters.

Coagulation factor assay with the conserved serum during the clinical course showed that FVIII levels measured 3 months before the diagnosis of AHA were already slightly decreased to 77% at day 117 compared with 97% measured at day 76 in association with an increase in fBP180 titres (Fig. S1[1]), hence the patient would have generated FVIIIis at the earliest 3 months before onset of oral bleeding. Importantly, production of those autoantibodies was synchronized with rapid tapering of prednisolone and withdrawal of DPP-4is.

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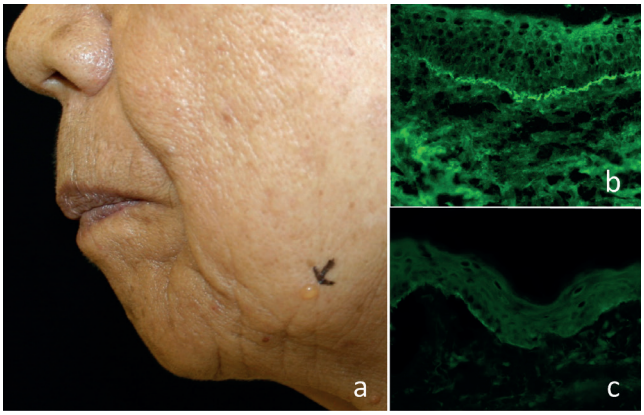

Fig. 1. (a) Clinical manifestations and histology of bullous pemphigoid localized on the cheek. (b) Direct immunofluorescence revealed linear deposit of C3 at the basement membrane zone. (c) Indirect immunofluorescence of patient's sera showed immunoglobulin (Ig)G-positive reactivity at a titre of 1 in 5, which localized to the epidermal side of 1M NaCl-split-skin. Original magnification (b) ×100; (c) ×200.

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DISCUSSION

AHA is a well-documented complication of BP that occurs at any time after onset of BP during the treatment course, although no associations between DPP-4is and onset of AHA have been reported. However, according to a recent review (4), the majority (39.1%) of patients are likely to develop AHA 2–6 months after the onset of BP. The time between BP onset and AHA onset was 7 months in the current case, and ranged from 0 to 2 years in previously reported cases. These results suggest that the timing of withdrawal or tapering of immunosuppressive agents (prednisolone) may be critical in determining whether AHA will develop in patients with BP. Thus immune recovery that occurs shortly after withdrawal or tapering of prednisolone doses might have a strong impact on the subsequent development of AHA (9). In this regard, given that DPP-4 is also known as a T-cell activation antigen, CD26, and is highly expressed on activated T cells, particularly Th1 and Th17 cells (10), it is likely that patients treated with DPP-4is could be in an immunosuppressive state. Indeed, recent reports have demonstrated a significant reduction in the number of CD4+ T cells in diabetic patients treated with DPP-4is (11). Diabetic patients treated with DPP-4is could be at great risk of developing the wide spectrum of immune reconstitution inflammatory syndrome (IRIS): IRIS is an increasingly recognized disease concept, ranging from CMV disease and autoimmune disease upon cessation or reduction of immunosuppressive agents, such as DPP-4is and prednisolone. Thus, we can hypothesize that rapid and abrupt immune restoration/recovery from an immunosuppressive state could provide a mechanism for the development of autoimmune disease. Given the immunosuppressive properties of DPP-4is, and taking into consideration the timing of the onset of AHA after withdrawal of both DPP-4is and prednisolone, an association between AHA onset and immune reconstitution could be postulated in our patient (12). It is therefore possible that withdrawal of prednisolone, acting synergistically with DPP-4is cessation, may have contributed to the onset of AHA in the current patient.

Although underlying aetiology, age, and sex do not influence time to remission (13, 14), AHA occurring in patients with DPP-4is-associated BP may require longer to eradicate the FVIIIis and to restore normal FVIII levels, given that complete remission did not occur long after cessation of DPP-4is and prolonged treatment with prednisolone in the current case. At present, no data are available on the efficacy of systemic corticosteroids in patients with BP with DPP-4is-associated AHA compared with other aetiologies.

In conclusion, clinicians should be aware that secondary autoimmune disease, including AHA associated with epitope/antigen spreading, may occur in patients with BP receiving DPP-4is, upon cessation of DPP-4is and withdrawal of systemic corticosteroids. In cases in which recent onset of abnormal bleeding is suspected, especially, in elderly patients, AHA should be considered and prompt monitoring of FVIIIis and FVIII levels is recommended.

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