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CORRESPONDENCE

A case of bullous pemphigoid after a long-term administration of anti-PD-1 antibodies in a patient with non-small-cell lung cancer

We described a case of BP that developed 2.5 years after the administration of nivolumab for metastatic non-small cell lung cancer. Our report highlights the fact that dermatologists should be aware of anti PD-1-related BP, which can appear very late during treatment.

Dear Editor,

Bullous pemphigoid (BP) secondary to antiprogrammed death 1 (PD-1) antibodies has been increasingly reported. Bullae usually develop within the first 6-8 months of the initiation of anti-PD-1 antibodies, although a smaller subset of patients developed bullae 1-1.5 years later.[1] We report a case of BP that developed 2.5 years after the administration of nivolumab for metastatic non-small-cell lung cancer (NSCLC).

A 64-year-old Japanese man with metastatic NSCLC presented for the evaluation of pruritic vesicles and blisters. He had received nivolumab (2 mg/kg) every 2 or 3 weeks, with 47 cycles over a period of two and a half years, resulting in a partial response. However, he developed severe itching 6 months prior to his current presentation to our clinic and blisters appeared on his lip and extremities 1 month prior to presentation. His medical history included myocardial infarction and type 2 diabetes. He took insulin treatment at the same time as nivolumab therapy was commenced. Physical examination revealed erythematous patches and multiple tense blisters and erosions on his lip, extremities, and abdomen (Figure 1A-C). Skin biopsy from the abdominal blisters showed subepidermal blisters with mixed infiltration of eosinophils and lymphocytes (Figure 1D). Direct immunofluorescence revealed linear basement membrane zone (BMZ) deposits of IgG and C3 (Figure 1E). Indirect IF on normal human skin revealed IgG anti-BMZ antibodies (Figure 1F). Immunoblotting revealed positive IgG and negative IgA reactivity with recombinant proteins of the BP180-NC16a domain (Figure 1G). Chemiluminescent enzyme immunoassay for BP180 was 55 U/mL. These findings were consistent with BP. The BP disease activity index (BPDAI) was 8 for erosions/blisters and 7 for urticaria/erythema. He was treated with topical steroids, which resulted in his symptoms worsening: BPDAI was 28 for erosions/blisters and 22 for urticaria/erythema. Therefore, treatment with oral prednisolone 15 mg/day and minocycline 100 mg/day was initiated. Additionally, his nivolumab therapy remained ongoing. With this regimen, his BPDAI decreased to 1 after 4 weeks. Two years later, BP was controlled with prednisolone 6 mg/day. He currently is still receiving nivolumab without NSCLC progression.

Paraneoplastic BP is characterized by both remission of symptoms after the treatment of tumor and reappearance of BP lesions with cancer recurrence.[2] In this case, lung cancer was completely resolved at the onset of BP, and neoplastic BP could be ruled out. We diagnosed nivolumab-induced BP. Anti-PD-1 antibody-induced BP with a late onset of over 1 year was previously reported in five cases,[1,3] all of whom were males ranging in age from 58 to 80 years. Three of the patients were lung cancer cases, and two had melanoma. The symptoms developed 52-84 weeks after the initiation of anti-PD-1 antibody therapy. Compared with other immune-related adverse events, BP-like eruptions have a delayed mean onset of 13-15 weeks after treatment initiation.[4] In contrast to classic idiopathic BP, anti-PD-1-related BP might be more likely to exhibit atypical features, such as prolonged pruritus and nonbullous eruption.[5] Our report highlights the fact that physicians should be aware of anti-PD-1-related BP, which can appear very late during treatment.

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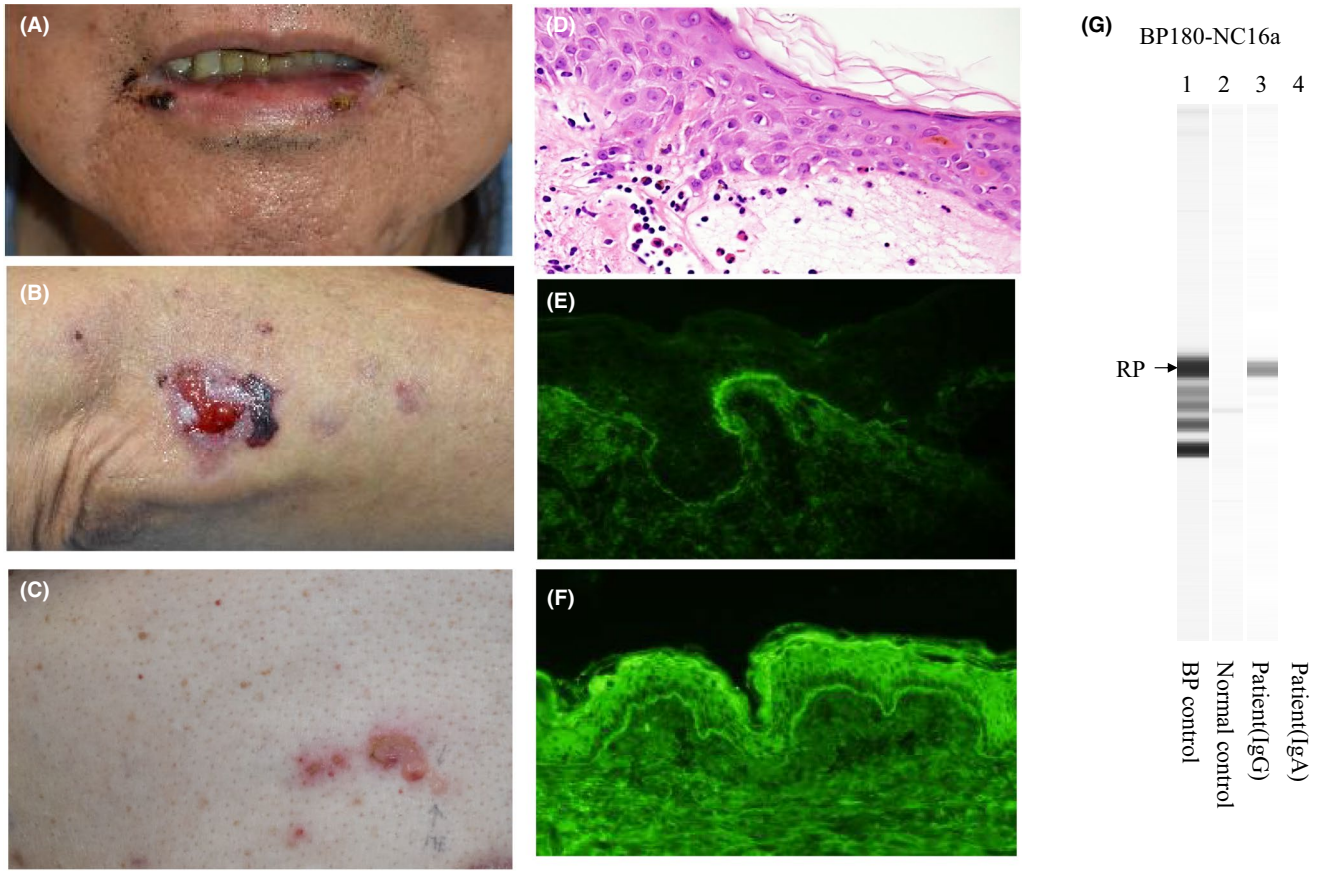

FIGURE 1 (A) Multiple bullae and crusts on the lower lip. (B) Tense blisters and erosions on the upper limbs. (C) Erythematous and vesicles on the abdomen. (D) Subepidermal blister with infiltration of eosinophils and lymphocytes (hematoxylin-eosin stain ×400). (E) Direct immunofluorescence showed a linear deposition of IgG on the basement membrane zone. (F) Circulating IgG autoantibodies were detected by indirect immunofluorescence of normal human skin. (G) Immunoblot method using human epidermal extract and the NC16a site recombinant protein of BP180 was IgG-positive and IgA-negative, which are typical findings of bullous pemphigoid

DECLARATION SECTION

Approval of the research protocol: N/A.

Informed Consent: The written informed consent was obtained from the patient.

Registry and the Registration No. of the study/trial: N/A.

Animal Studies: N/A.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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