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Nivolumab-Induced Bullous Pemphigoid Managed without Drug Withdrawal

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Abstract

The widespread use of anti-programmed cell death receptor-1 (PD-1) agents has shed light to unusual immune-related adverse effects, especially affecting the skin. We report a case of bullous pemphigoid secondary to nivolumab therapy for metastatic renal carcinoma with a previously unreported complete response to clobetasol ointment alone. The autoimmune blistering disease was successfully treated without oral corticosteroids, and the anti-PD-1 agent could be maintained without recurrence of the skin lesions. Topical therapy remains a good option in selected, mild-to-moderate cases of induced bullous pemphigoid.

Key Words: *Anti-programmed cell death receptor-1*, *bullous pemphigoid*, *nivolumab*, *renal carcinoma*, *topical treatment*

Introduction

Immune checkpoint inhibitors, such as nivolumab, have revolutionized the treatment of some metastatic tumors, such as melanoma or lung cancer. However, up to 40% of patients may develop immune-related adverse events affecting the skin.[1] Autoimmune blistering diseases have infrequently been described.

We report a case of bullous pemphigoid appeared shortly after the second dose of nivolumab and managed without drug withdrawal.

Case Report

A 62-year-old man presented at our department with a 1-month history of a generalized and pruritic eruption. The patient had no previous history of autoimmune or inflammatory skin conditions. Medical history was significant for metastatic renal carcinoma previously treated with sunitinib and everolimus, none of which were effective. Treatment with nivolumab (3 mg/kg intravenously every 2 weeks), started 1 month before the eruption, achieved a good response of his oncologic disease.

On examination, the skin showed numerous hemorrhagic crusted papules and plaques especially affecting the trunk [Figure 1a], and two active bullous lesions were present on the dorsum of his right arm [Figure 1b]. Skin biopsy of an intact lesion showed a subepidermal blister [Figure 2a] with a dermal

lymphocytic infiltrate with numerous eosinophils [Figure 2b]. A linear deposition of C3 (+++) and immunoglobulin G (++) at the dermo-epidermal junction was shown on direct immunofluorescence [Figure 2c]. The enzyme-linked immunosorbent assay for BP180 autoantibody was positive, with a negative BP230. These changes were consistent with the clinical impression of bullous pemphigoid.

As the patient had shown good response and the adverse event was tolerable, nivolumab was maintained, and treatment for bullous pemphigoid was started with clobetasol ointment followed by a progressive reduction to a weekly maintenance therapy. The response was complete with topical steroid. No relapse was observed with the following nivolumab administrations.

Discussion

Nivolumab is a monoclonal antibody that specifically targets the programmed cell death receptor-1 (PD-1), thus improving the T-cell-mediated antitumor response. Dermatologic toxicities are among the more frequent adverse events of these drugs.[2]

To our knowledge, more than 20 cases of bullous pemphigoid in patients receiving anti-PD-1 agents have been reported, 10 of them induced by nivolumab, 12 by pembrolizumab, and 1 by durvalumab.[1,2,3,4,5,6,7] The association of bullous pemphigoid with cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) inhibitors, such as ipilimumab remains controversial, as reported cases appeared in association with anti-PD-1 therapy, but no cases have been reported with CTLA-4 inhibitors alone.[2] While bullous pemphigoid has mostly been described in the setting of immunotherapy for metastatic melanoma, lung cancer, and urothelial carcinoma,[2] there is only one other case reported in a patient with metastatic renal carcinoma, which required drug withdrawal.[8]

Although pathogenesis is not fully understood, it is hypothesized that anti-PD-1/programmed cell death ligand-1 (PD-L1) blockade may result in a loss of tolerance and the development of T-cells against BP180. Moreover, a humoral response may result from the activation of B-cell germinal center secondary to an interaction between PD-1/PD-L1 expressing B-cells and PD-1+ follicular helper cells.[9]

A potential association between bullous pemphigoid with an improved survival in patients receiving anti-PD-1 inhibitors has been suggested. However, response rates in these patients (41.7%) seem to be similar to that reported in the literature, and induced-bullous pemphigoid does not seem to be a marker of a better response.[2,4]

The persistence and the severity of bullous pemphigoid lesions led to therapy discontinuation in previous reports.[2,4,7,9] In general, treatment includes topical and oral steroids,[2] but other therapies, including omalizumab[4] and rituximab,[6] have also been used. In our case, nivolumab could be maintained as clobetasol ointment alone achieved a complete response.

Conclusion

As new indications of anti-PD-1 therapies in other neoplasms arise, an increase is expected in the number of immune-related adverse events, including autoimmune skin diseases. Thus, awareness and close monitoring of dermatological toxicities is crucial to ensure an adequate management. Immunotherapy withdrawal is not always mandatory and should be individualized. Topical therapy remains a good option in selected, mild-to-moderate cases.

Declaration of patient consent The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest There are no conflicts of interest.

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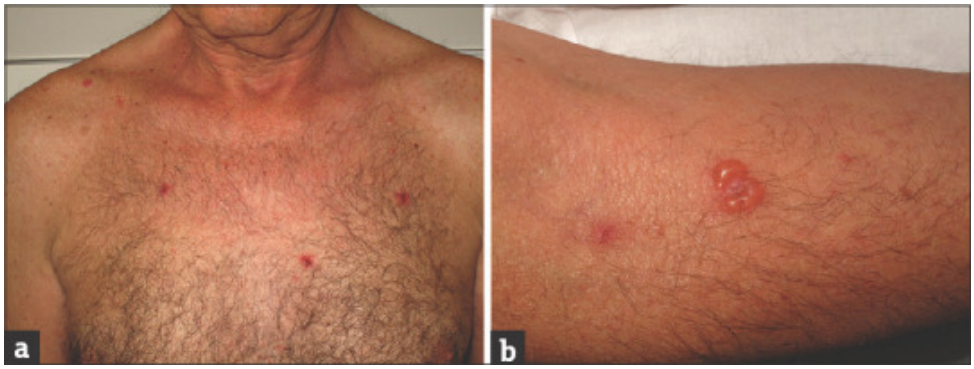
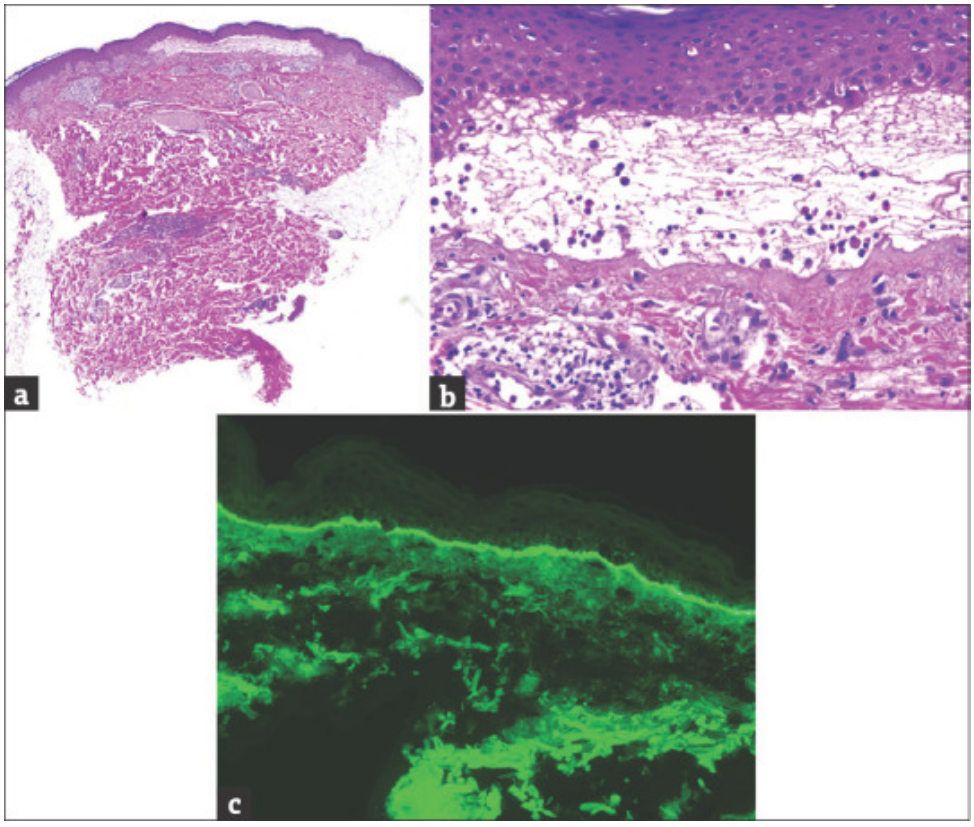
Figures and Tables

Figure 1



Clinical features. Crusted papules and plaques on the trunk (a) and active bulla on the right arm (b)

Figure 2



Histopathological and immunological features. Histopathological features include a subepidermal blister (H and E, ×40) (a) with eosinophil infiltration (H and E, ×200) (b). Direct immunofluorescence for C3 shown linear deposition at the dermal-epidermal junction (Immunofluorescence stain, ×100) (c)