BRIEF ARTICLES

Development of Bullous Pemphigoid While Receiving PD-1 Checkpoint Inhibitor Nivolumab

ZP Nahmias MD[a], ED Merrill[b], CC Briscoe JD[a], CE Mount MD[c], S Abner MD[a], A Schaffer MD PhD[a], MJ Anadkat MD[a]

[a]Washington University School of Medicine, St. Louis, MO
[b]University of Missouri-Kansas City School of Medicine, Kansas City, MO
[c]Allegheny General Dermatology, Pittsburgh, PA

ABSTRACT

Monoclonal antibodies against PD-1 are becoming increasingly important agents in the oncologist's armamentarium against a variety of cancers, including melanoma and squamous cell carcinoma. Most reported cutaneous reactions to these agents are mild and resolve with a conservative treatment approach. We present two cases of patients treated with anti-PD-1 agents who developed bullous pemphigoid shortly after initiation of therapy. We then review the literature of anti-PD-1-associated bullous pemphigoid, which is likely a bona fide side effect of anti-PD-1 therapy. Finally, we discuss management of these cases, where the risks of bullous pemphigoid must be weighed against the benefits of anti-PD-1 treatment. As the number of indications for PD-1 monoclonal antibodies expands, dermatologists will need to recognize their cutaneous adverse events and assist oncologists in the management of such complications.

INTRODUCTION

Monoclonal antibodies (mAb) targeting components of cell cycle regulation are a proven modality for the treatment of cancer. Blockade of the programmed death-1 (PD-1) pathway provides a treatment arm for some cases of metastatic disease. Nivolumab and pembrolizumab are humanized IgG4 anti-PD-1 monoclonal antibodies. Blockade occurs via programmed death-ligand 1 to PD-1 on cells, a process that facilitates activation of T lymphocytes, allowing the immune system to attack cancerous cells.[1]

More than 40% of melanoma patients treated with anti-PD-1 therapy develop dermatologic complications.[2] The cutaneous manifestations associated with anti-PD-1 therapy are generally self-limited and mild and can be managed conservatively. The most commonly reported cutaneous side effects in melanoma patients were a nonspecific macular and papular rash with pruritus, a lichenoid or psoriasiform drug eruption, and vitiligo.[2] Development of blistering disease associated with the use of anti-PD-1 therapy has not commonly been

reported to date; however, recent reports that bullous pemphigoid (BP) may be a rare side effect of anti-PD-1 therapy continue to accumulate. In this review, we present two patients who developed BP shortly after starting nivolumab. We then review the literature of anti-PD-1-associated BP. A discussion of management and treatment options follows.

CASE SERIES: PATIENT 1

An 80-year-old white male presented with stage IV cutaneous squamous cell carcinoma with disease burden in the axillary lymph node basin, lungs, mediastinum, pleura, and liver. He had previously failed three months of therapy with carboplatin, paclitaxel, and cetuximab, and was subsequently started on nivolumab. Seven months later, the patient developed a pruritic rash on his trunk and extremities that was histopathologically consistent with a lichenoid drug eruption. He was treated with topical triamcinolone ointment 0.1% and clobetasol ointment 0.05%.

Six weeks later, the patient presented with bullae clinically consistent with BP (Figure 1). Biopsy confirmed BP with blister cavities, eosinophils, and strong linear deposition of C3 at the dermal-epidermal junction. Nivolumab was discontinued and, given his multiple comorbidities, he was treated with a steroid taper and dapsone. After several weeks of treatment with dapsone, he developed a hemolytic anemia and this agent was discontinued. The BP remained controlled on 10 mg prednisone daily with sporadic use of topical clobetasol. Five months after discontinuation of nivolumab, the patient was stable without evidence of disease progression.

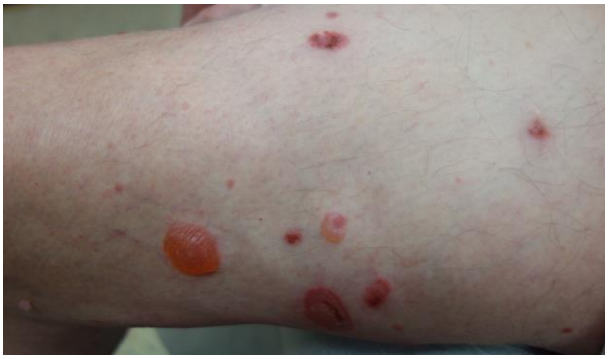

Figure 1. Tense fluid-filled blisters with an erythematous underlay and several crusted papules and excoriations present on the extremities

CASE SERIES: PATIENT 2

An 85-year-old white male undergoing treatment for metastatic BRAF-negative melanoma developed non-pruritic blisters on his trunk and extremities 8 to 9 weeks after starting nivolumab. The blisters were tense and clinically consistent with BP (Figure 2).

Initial biopsy was equivocal, but repeat biopsy during a time of relative flaring was consistent with BP on both H&E and DIF. The patient substantially improved following discontinuation of nivolumab therapy. The addition of dapsone and topical clobetasol

ointment 0.05% significantly improved the extent and severity of his rash. The burden of his BP is currently limited to minimal red patches with no bullae present, and a dapsone taper is planned.

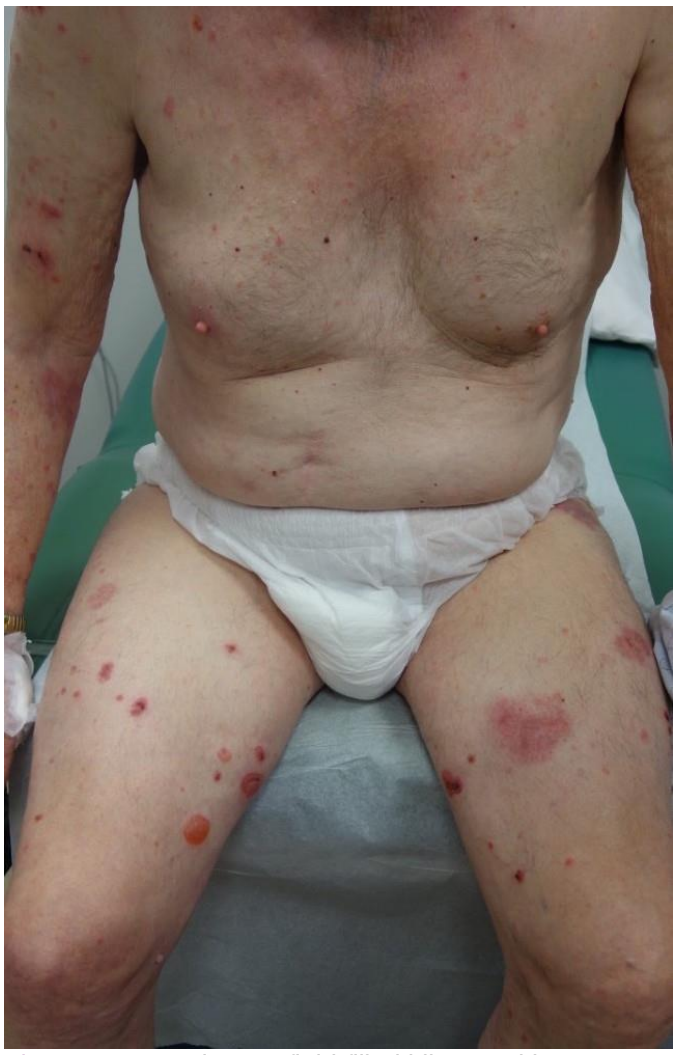

Figure 2. Several tense fluid-filled blisters with crusted pink papules and red plaques diffusely on the body

DISCUSSION

When combined with the existing literature, these two cases add to a growing body of evidence surrounding a unique side effect of PD-1 antagonists (Table 1). To date, the most common cutaneous adverse events associated with these agents are a nonspecific macular and papular rash or a lichenoid eruption.[2] Keen clinical judgment is needed given the numerous variables involved, including the timing of the rash in the treatment course, the clinical status of the patient, any known allergies or previous adverse drug reactions, and the likelihood of successfully managing the rash. Recognizing the development of a blistering disease as a distinct entity separate from drug-induced dermatitis is important, as a change in cancer therapy may be indicated depending on its severity.

Our patients add to the previous literature and combine for a total of 18 cases of PD-1 antagonist-associated BP (11 nivolumab, 6 pembrolizumab, 1 durvalumab). The median age of patients was 73.5 (range of 42 to 85), and the median number of weeks of anti-PD-1 treatment prior to onset of BP was 17 (range of 3 to 91). Before developing BP, many patients had earlier cutaneous symptoms, such as a pruritic maculopapular rash or a lichenoid drug eruption.

Table 1. Details of 18 reported cases of bullous pemphigoid developing in the setting of PD-1 checkpoint inhibitor therapy

Age/Sex/Agent/BP onset (weeks)	BP progression	Disease progression
80s/M/Nivo[3]/80	Improved with oral steroids, flared after cessation; resolution on rituximab	Remission for 8 months after discontinuing Nivo
77/F/Nivo[4]/6	Improved with topical and oral steroids; Nivo restarted with omalizumab	None reported
80/M/Nivo[5]/24	BP flared after each Nivo dose, requiring cessation at 52 weeks	Remission 5 months following Nivo discontinuation
85/M/Nivo[5]/18	BP continued for 10 months following Nivo discontinuation	Stable disease at 15 months after discontinuation of Nivo
60/M/Nivo[6]/12	BP resolution in 2 weeks with steroids	None reported
63/M/Nivo[7]/14	Improvement when Nivo held; relapse with rechallenge led to discontinuation	Progression at 5 weeks
74/F/Nivo[7]/16	Progressive improvement of BP at 3 weeks without recurrence	Partial response despite discontinuation
73/F/Nivo[7]/7	Improved with oral steroids; progressed on steroid-sparing agents and topical steroids, leading to Nivo being withheld	Disease progression
59/M/Nivo[7]/3	Resolution within 2 weeks of IV steroids	Disease progression
80/M/Nivo/35 (current report)	Stable on steroids with no progression 5 months after discontinuation of Nivo	No progression 5 months after discontinuation of Nivo
85/M/Nivo/9 (current report)	Improved with steroids, dapsone, and Nivo discontinuation	None reported
63/M/Pembro[8]/91	Controlled with steroids until Pembro stopped due to complete response	In remission 9 months following Pembro discontinuation
42/M/Pembro[9]/48	Improved with steroids, nicotinamide, and doxycycline	Minimal activity on restaging
68/M/Pembro[7]/16	Rapid improvement with oral steroids	Melanoma progression
68/M/Pembro[10]/78	Resolution at 5 weeks with topical steroids and discontinuation of Pembro	Sustained partial response from week 15 of treatment
72/M/Pembro[10]/18	Well-controlled with steroids and methotrexate	Melanoma progression
75/M/Pembro[11]/7	Resolved with oral steroids	Melanoma progression
78/F/Durva[5]/52	Continued, isolated BP for 1 year after Durva stopped despite topical steroids	Partial response

F = female; M = male; BP = bullous pemphigoid; Nivo = nivolumab; Pembro = pembrolizumab; Durva = durvalumab; IV = intravenous.

Treatment regimens have included a combination of oral and topical corticosteroids, often in conjunction with discontinuation of the anti-PD-1 therapy. In situations where the anti-PD-1 therapy is ineffective and did not achieve the desired result, discontinuation is clearly warranted. However, in the context of a clinical response to anti-PD-1 therapy, discontinuing the agent is challenging, and the risks of continued treatment must be carefully weighed against its benefits. As a further complication, treatment with corticosteroids is potentially problematic when using anti-PD1 agents due to the theoretical risk of diminishing the immunomodulatory actions of such drugs.

Topical steroids are generally first-line treatment for BP and are largely safe due to their limited systemic absorption. In contrast, some authors have avoided prolonged use of systemic corticosteroids given their adverse effects. In one case, the authors avoided systemic corticosteroids by using rituximab, which was started after discontinuation of nivolumab and led to resolution of BP.[3] In another, the authors were able to reintroduce nivolumab with concurrent omalizumab while using systemic steroids to control the patient's BP.[4] Future studies are needed to better define the efficacy of using targeted immunotherapy alongside anti-PD-1 treatment.

With an increasing number of indications for treatment, use of anti-PD-1 agents by oncologists and dermatologists will become increasingly common. Individuals with metastatic disease who have failed one or more therapies frequently have several comorbidities associated with their primary oncologic process, further complicating management considerations. The population at risk for BP is also elderly and therefore at an increased risk for comorbid conditions like hypertension, thromboembolism, and cardiovascular disease.[12] Going forward, dermatologists will play a critical role in the management of patients taking anti-PD-1 agents, as optimizing quality of life and treatment will need to take into account each patient's cutaneous adverse effects within the context of a broader medical picture.

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Corresponding Author:
Cristopher C. Briscoe, JD
660 S. Euclid Ave
Campus Box 8123
St. Louis, MO 63110
314-362-9859 (Office)
briscoec@wustl.edu

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