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irAEs

A Case of Nivolumab-Induced Bullous Pemphigoid: Review of Dermatologic Toxicity Associated with Programmed Cell Death Protein-1/Programmed Death Ligand-1 Inhibitors and Recommendations for Diagnosis and Management

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Abstract

Immunotherapy has emerged as a highly effective treatment for numerous cancers. Use of checkpoint inhibitors against various molecules including programmed cell death protein-1 (PD-1), programmed death ligand-1 (PD-L1), and cytotoxic T-lymphocyte-associated protein-4 have become widespread in clinical practice. Compared with conventional chemotherapy, immunotherapy is associated with a unique set of immune reactions known collectively as immune-related adverse events (irAEs). Of known irAEs, cutaneous toxicity is among the most frequently observed in patients treated with immunotherapy. Although often mild, dermatologic toxicity can occasionally be high grade and potentially life-threatening. In this article, we report a case of PD-1 inhibitor-induced bullous pemphigoid—a serious adverse event that has been increasingly observed with use of PD-1/PD-L1 inhibitors. We will also review diagnosis and management of low-grade cutaneous irAEs and bullous disease with checkpoint inhibitors. ***The Oncologist*** 2018;23:1119–1126

Key Points

- PD-1/PD-L1 inhibitor-induced bullous pemphigoid (BP) is a rare but potentially serious dermatologic toxicity associated with checkpoint inhibitors
- In patients with pruritus or rash that is refractory to topical steroids, physicians should have a greater index of suspicion for higher-grade cutaneous immune-related adverse events.
- There is no standardized treatment algorithm for management of PD-1/PD-L1 inhibitor-induced BP, but patients frequently require topical and systemic steroids.

Introduction

Immune checkpoint inhibitors have rapidly become first-line therapy for a variety of advanced malignancies. Monoclonal antibodies against programmed cell death protein-1 (PD-1) and programmed death ligand-1 (PD-L1) have demonstrated durable anticancer effects and have drastically improved patient outcomes for several cancers [1–4]. Although these drugs have been associated with a number of adverse events (AEs), cutaneous immune-related adverse events (irAEs) are among the most common [5].

Bullous pemphigoid (BP) is an autoimmune subepidermal blistering disease characterized by the development of tense bullae and is most frequently seen in the elderly. PD-1/PD-L1-induced BP has recently emerged as a potentially serious dermatologic toxicity and has been observed with some degree of frequency. Herein, we report a case of a 72-year-old woman who developed BP shortly after initiating treatment with PD-1 inhibitor nivolumab for metastatic non-small cell lung cancer (NSCLC). In addition to adding to the existing literature regarding PD-1 inhibitor-induced BP, we will use this case to highlight diagnosis and management of cutaneous irAEs associated with checkpoint inhibitors.

Case Report

A 72-year-old woman with metastatic NSCLC presented for evaluation of new onset pruritic blisters. Three months prior, the patient was found to have a 4-cm right upper lobe lung mass and numerous smaller pulmonary nodules during a workup for progressive dyspnea. Percutaneous biopsy at that time demonstrated CK5/p40-positive and PD-L1-negative squamous cell carcinoma (SCC).

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Positron emission tomography-computed tomography revealed an FDG-avid soft tissue prominence between ribs 11 and 12 as well as FDG-avid nodular thickening of the left adrenal gland, which were suspicious for metastasis. Past medical history was notable for a remote history of laryngeal SCC successfully treated with chemoradiation, complicated by partial vocal cord paralysis and tracheoesophageal fistula requiring tracheostomy and percutaneous endoscopic gastrostomy placement.

The patient declined chemotherapy but was amenable to treatment with immunotherapy and was started on intravenous nivolumab 3 mg/kg every 2 weeks. Following her first infusion, the patient noted new onset of generalized itching. Symptoms peaked immediately after infusion and improved over the following days to week until her second infusion, when symptoms again increased after treatment, following a similar pattern. Following cycle 3, the patient reported worsening pruritus and was found to have new blisters on her arms and legs. She was thus promptly referred to our clinic for evaluation.

On exam, there were numerous superficial erythematous erosions and tense blisters on chest, arms, legs, and abdomen (Fig. 1). There was no involvement of palms or mucosal surfaces. Two 3.0-mm punch biopsies of the lower leg were performed and sent to pathology for evaluation by hematoxylin and eosin (H&E) and immunofluorescence. H&E stain was remarkable for a perivascular lymphocytic and eosinophilic infiltrate, which was consistent with subepidermal bullous dermatitis. Direct immunofluorescence (DIF) showed linear IgG and C3 along basement membrane zone, confirming the diagnosis of BP.

The patient was started on 60 mg of oral prednisone daily and topical clobetasol 0.05% cream twice daily, and nivolumab therapy was held. After 2 weeks of therapy with systemic steroids and high-dose topical steroids, the prednisone dose was decreased to 50 mg/day as new blister formation ceased and the patient had marked improvement in pruritus and existing skin lesions. However, she subsequently developed recurrence of blisters/pruritus, and oral prednisone was increased back to 60 mg/day. In addition, the patient was also started on oral minocycline 100 mg/day and oral niacinamide 500 mg/day as adjunctive therapies. The patient was maintained on this regimen for 6 weeks, after which steroid taper was successful without BP recurrence. Following goals of care discussions, nivolumab therapy was not restarted.

Discussion

Within the past several years, our increased understanding of tumor immunity has led to the successful development of immunotherapy and has completely transformed the field of cancer therapeutics. Immune checkpoint inhibitors targeting PD-1/PD-L1 and cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) have demonstrated exceptional antitumor activity in numerous solid and hematologic malignancies, resulting in marked survival benefits [1–4]. Ipilimumab, an anti-CTLA-4 monoclonal antibody, was the first U.S. Food and Drug Administration-approved immunotherapy in 2011 for metastatic melanoma [6]. Following this, agents targeted against other immune checkpoint molecules, including PD-1 inhibitors pembrolizumab and nivolumab, have since become first-line therapies for advanced melanoma and NSCLC [7]. As a result, research to evaluate the efficacy of checkpoint inhibitors in other cancers has exploded, with a push to expand approved indications of use [8, 9]. With anticipated growth in the number of patients eligible to receive checkpoint inhibitor therapy, it is critical for physicians to be familiar with associated drug toxicities and management.

Panel 1: Rare severe cutaneous toxicities associated with programmed cell death protein-1 inhibitors

- Stevens-Johnson syndrome
- Erythema multiforme
- Drug rash with eosinophilia and systemic symptoms (DRESS syndrome)
- Bullous pemphigoid

Increased use of checkpoint inhibitors has revealed a unique set of inflammatory toxicities termed irAEs. Although the mechanism of irAEs is incompletely understood, it is widely believed that most irAEs develop secondary to nonspecific activation of the immune system [10]. Checkpoint inhibitors work primarily by restoring antitumor immune responses by disrupting coinhibitory T-cell signaling. Overexpression of PD-L1 by tumor cells is a major mechanism of tumor immune evasion via inhibition of T cell function [11]. Its receptor, PD-1, is primarily found on regulatory T cells (Tregs), which foster a highly immunosuppressive environment by attenuating the immune response. In contrast, CTLA-4 is expressed widely by T cells and interacts with its ligand on antigen-presenting cells during the early phase of immune response [12]. The CTLA-4 immune checkpoint functions to upregulate the immunosuppressive activity of Tregs and downregulate CD4+ T effector cells, resulting in a global impact on immune tolerance [13]. Although blocking these pathways with checkpoint inhibitors results in profound antitumor effects, the PD-1/PD-L1 and CTLA-4 pathways are both crucial for the maintenance of normal immunologic homeostasis [14]. Therefore, dysregulation of these pathways can impair peripheral tolerance and alter the delicate balance within the immune system, resulting in the development of off-target effects and autoimmunity. Risk factors for development of severe irAEs include personal or family history of autoimmune diseases, brisk inflammatory response at the tumor site, and concomitant use of medications with known autoimmune toxicities [15].

Although there are a wide range of known irAEs associated with anti-PD-1/PD-L1 and anti-CTLA-4 therapy, cutaneous AEs are among the most commonly observed toxicities associated with checkpoint inhibitors [16]. Although the majority of cutaneous irAEs are mild or moderate, checkpoint inhibitor-induced BP has emerged as a rare but serious potential cutaneous AE of checkpoint inhibitor therapy. Other potentially severe cutaneous irAEs that have been associated with anti-PD-1 inhibitor therapy include Stevens-Johnson Syndrome, erythema multiforme, and drug rash with eosinophilia and systemic symptoms (DRESS syndrome; Panel 1) [17–20]. If left untreated, these dermatologic conditions can result in significant morbidity and may even be life-threatening.

To date, 22 cases of BP associated with PD-1/PD-L1 inhibitors have been reported in the literature [21–36]. In contrast, BP associated with anti-CTLA-4 therapy has only been reported in two cases, suggesting this irAE is more specific to anti-PD-1/PD-L1 therapy [37, 38]. Although the mechanism of PD-1/PD-

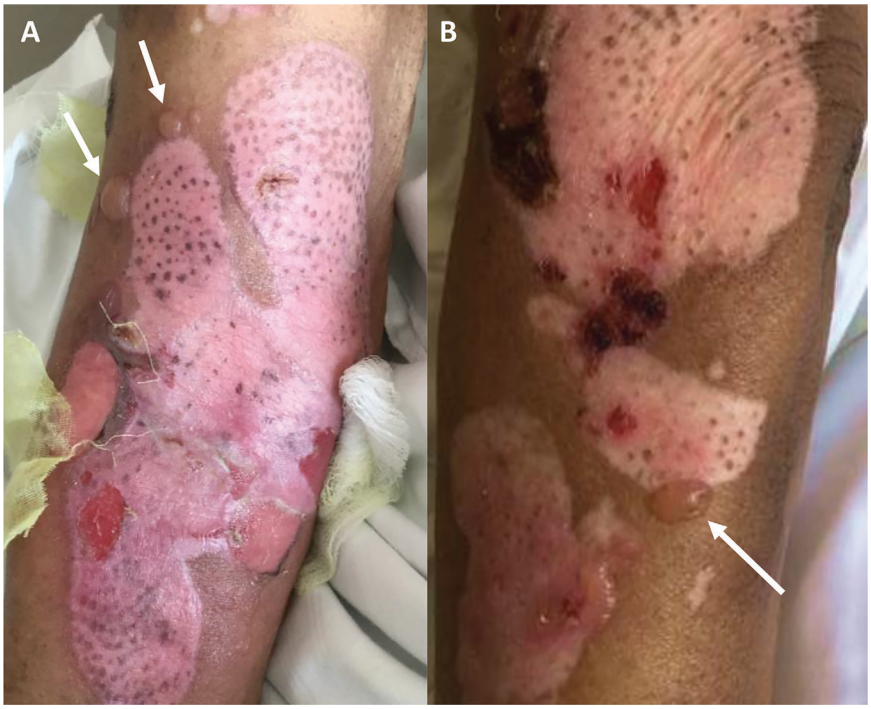

Figure 1. Tense bullae (arrows), erythematous superficial erosions, and healing ulcers on the right arm **(A)** and left leg **(B)**. Re-epithelialization and repigmentation is present in the areas of former blisters.

L1 inhibitor-induced BP is unknown, it is thought to be driven by autoantibody production against hemidesmosomal structural proteins BP180 and BP230 [36, 39]. Although this is the same pathomechanism believed to cause conventional BP, it is unclear how anti-PD-1/PD-L1 immunotherapy facilitates this reaction. Of reported cases, BP most frequently developed within the first 6–8 months of treatment; however, a smaller subset of patients did not present until 1–1.5 years later [27, 31]. In many patients, development of bullae was preceded by prodromal pruritus and nonspecific rash, as observed in this case [23–26, 28, 30–32, 34–36].

Making the diagnosis of BP can be challenging, as its clinical presentation is heterogeneous. In some instances, pruritus may be the predominant symptom and blisters or rash may never develop [40]. In addition, pruritus is one of the hallmark symptoms of the prodromal BP phase, which can precede the development of bullae by weeks to months [41]. Unfortunately, pruritus is also one of the most commonly observed low-grade AEs with PD-1 inhibitors and has been reported in approximately 15%–30% of patients [1, 42–45]. Although new onset pruritus with PD-1 inhibitor therapy is not usually a harbinger of severe cutaneous toxicity, there are currently no predictive biomarkers to aid in the diagnosis of irAEs [46–48]. Therefore, differentiating PD-1 inhibitor-induced BP from other low-grade cutaneous toxicity is not always straightforward, and biopsy is generally required. Diagnosis can be confirmed with DIF on perilesional skin biopsy. Although DIF is the gold standard for the diagnosis of BP, serum testing via indirect immunofluorescence and enzyme-linked immunosorbent assay can be useful in combination to support the diagnosis of BP in a patient in whom clinical and histopathologic features suggest BP but DIF is negative [49, 50].

In addition to distinguishing prodromal BP from other common AEs, differentiating drug-induced BP from idiopathic BP in the elderly can be difficult, as the vast majority of idiopathic cases of BP occur in individuals over the age of 60 [51]. The clinical picture is further complicated in oncologic populations in which some evidence suggests BP can arise as a paraneoplastic condition, although this is controversial [52, 53]. However, the numerous reports of BP arising in the setting of PD-1 inhibitor therapy has served to strengthen the association between medication exposure and development of this autoimmune disease [21–36]. In this case, our patient developed BP 7 weeks after initiation of therapy with nivolumab. Given the temporal relationship between initiation of immunotherapy and the onset of BP, paraneoplastic and idiopathic BP are less likely.

Although the incidence of high-grade cutaneous toxicity with PD-1 inhibitors is low (approximately 1%–2%), "rash," pruritus, and vitiligo are the three most common cutaneous toxicities observed with pembrolizumab and nivolumab [54]. In a recent meta-analysis of phase I–III monotherapy trials with nivolumab and pembrolizumab, the relative risk for developing any dermatologic AE for pembrolizumab or nivolumab was 2.95 and 2.3 respectively. All-grade incidence of rash with pembrolizumab was 16.7% (95% confidence interval [CI]: 11.9%–23.0%) and 14.3% (95% CI: 8.7%–22.7%) with nivolumab. The incidence of all-grade pruritus was also frequent calculated at 13.2% (95% CI: 8.9%–19.2%) and 20.2% (95% CI: 14.8%–26.9) for nivolumab and pembrolizumab, respectively. The observed incidence of vitiligo was reported to be 7.5% (95% CI: 5.9%–9.5%) with nivolumab and 8.3% (95% CI: 4.4%–15.2%) with pembrolizumab [54]. Interestingly, all AEs of vitiligo were noted in trials with patients being treated for melanoma, and it has been suggested as a prognostically favorable AE [42, 43, 55–57]. Although the evidence is mixed, development of cutaneous AEs for both pembrolizumab and nivolumab has been associated with longer progression-free survival when compared with those who did not experience cutaneous toxicity [58, 59].

Table 1. Descriptions of select cutaneous immune-related adverse events as defined by the CTCAE version 4.0

Symptom grade	Grade-specific descriptions			
	Skin hypopigmentation	Pruritus	Rash	Bullae
Grade 1	Hypopigmentation or depigmentation covering <10% BSA; no psychosocial impact	Mild or localized	Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	Asymptomatic; blisters covering <10% BSA
Grade 2	Hypopigmentation or depigmentation covering >10% BSA; associated psychosocial impact	Intense or widespread; intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); limiting instrumental ADL	Macules/papules covering 10%–30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL	Blisters covering 10%–30% BSA; painful blisters; limiting instrumental ADL
Grade 3	—	Intense or widespread; constant; limiting self-care/ADL or sleep	Macules/papules covering >30% BSA with or without associated symptoms; limiting self-care/ADL	Blisters covering >30% BSA; limiting self-care/ADL
Grade 4	—	—	—[a]	Blisters covering >30% BSA; associated with fluid or electrolyte abnormalities

[a]Grade 4 rash was removed from CTCAE version 4.0 and is therefore not defined.
Abbreviations: —, no data; ADL, activities of daily living; BSA, body surface area; CTCAE, Common Terminology Criteria for Adverse Events.

In general, PD-1/PD-L1 inhibitors have been associated with fewer side effects than anti-CTLA-4 therapy [60]. This can potentially be explained by greater T cell proliferation and reduced Treg-mediated immunosuppression with CTLA-4 blockade when compared with PD-1 inhibition [13]. Although anti-CTLA-4 therapy is associated with a myriad of irAEs, a pooled analysis of ipilimumab clinical trials demonstrated that dermatologic irAEs were the most common at 44.9% (all grade) [16]. This is of particular relevance as combination immunotherapy has become an emerging paradigm in cancer therapeutics. In particular, combination treatment with anti-PD-1 and anti-CTLA-4 therapies has become a hot area of research as synergistic effects may result in better outcomes [57, 61–63]. When ipilimumab is used in combination therapy, cutaneous toxicity has been reported to be as high as 64.3%, which is greater than the observed incidence of dermatologic toxicity of either agent alone [64]. Combination treatments of PD-1 inhibitors with ipilimumab have also shown relatively higher rates of grade 3–4 cutaneous toxicity [65]. Although this evidence suggests that cutaneous risk may be additive when ipilimumab is used in combination with PD-1/PD-L1 inhibitors, the relationship between irAEs and dose, duration of exposure, and drug combinations has yet to be fully elucidated [66].

Therapy for cutaneous irAEs is primarily based on grade severity. The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) is the most widely used severity grading scale for adverse event reporting in clinical trials. In the oncologic setting, "rash" may be used to encompass a myriad of cutaneous reactions. Released in 2009, CTCAE version 4.0 defines a variety of distinct dermatologic AEs that were not present in previous iterations (selected toxicities shown in Table 1) [67]. To better understand the cutaneous irAE profile of PD-1/PD-L1, providers should attempt to describe cutaneous reactions in as much detail as possible to best categorize the reaction. Although the majority of PD-1/PD-L1 clinical trial data does not provide more specific information regarding "rash" features, patient evaluation by dermatologists have described some of these cutaneous eruptions as eczema, lichenoid dermatitis, stomatitis, and urticaria [68, 69].

There is currently no standardized treatment for many irAEs, and recommendations are largely based on case reports, case series, personal experience, and expert consensus. Low-grade cutaneous toxicity associated with checkpoint inhibitors can generally be treated with topical steroids. In patients with pruritus or rash that is refractory to topical steroids, physicians should have a higher index of suspicion for higher-grade cutaneous irAE, and skin biopsy is recommended.

The treatment approach to checkpoint inhibitor-induced BP has largely been derived from studies conducted in patients with conventional BP. In a multicenter, randomized trial, 341 patients with BP were treated with either topical clobetasol propionate 0.05% cream (total 40 g/day over twice daily application) or oral prednisone (0.5 mg/kg/day for moderate disease or 1 mg/kg/day for severe disease). Both groups received treatment for 15 days after disease control and were tapered off topical and oral steroids until treatment was discontinued after 12 months. At study termination, they found that patients treated with clobetasol responded more quickly and had less severe/frequent complications than those treated with systemic steroids [70]. Although the findings of this study suggest that topical corticosteroids are preferable, systemic steroids are still highly effective and are widely accepted as another first-line therapy for BP in patients for whom topical corticosteroids are not practical or feasible. Although the optimal dosing of systemic steroids is unclear, studies suggest that 0.75–1.25 mg/kg/day of prednisolone (or steroid equivalent) is necessary to effectively control BP [71, 72]. In our experience, we have found monotherapy with high-dose topical

Table 2. Columbia University Cutaneous Oncology Center recommendations for management of Common Terminology Criteria for Adverse Events-based immune-related adverse events associated with immune checkpoint inhibitors

Severity grade	Assessment and management			
	Vitiligo	Pruritus	Rash	Bullae/blisters
Grade 1	Assessment: Full-body skin exam	Assessment: Mucocutaneous exam; rule out other causes (i.e., viral, contact dermatitis, other drug allergy)		Assessment: Nonacute dermatology referral recommended. Mucocutaneous exam, skin biopsy with DIF, serum for IIF, viral culture of blister base for HSV/VZV
	Management: Mid-high-potency topical steroids b.i.d., sun protection	Management: Low- to intermediate-strength topical steroids (i.e., triamcinolone 0.1% cream for body) b.i.d. and oral antihistamines (i.e., cetirizine/loratadine 10 mg/day). If no or minimal improvement after 2 weeks, reassess and consider referral to dermatology for punch biopsy		Management: High-dose topical corticosteroids (i.e., clobetasol 0.5% cream for body) while biopsy results are pending. Continue immunotherapy, but monitor closely for changes in severity
Grade 2	Assessment: Full-body skin exam	Assessment: Mucocutaneous exam; rule out other causes (i.e., viral, contact dermatitis, other drug allergy). Laboratory evaluation (LFTs, serum tryptase, IgE levels, CMP)		Assessment: Same-day dermatology referral. Mucocutaneous exam, skin biopsy with DIF, serum for IIF, viral culture of blister base for HSV/VZV
	Management: Mid-high-potency topical steroids b.i.d., sun protection. Encourage continuation of immunotherapy	Management: High-potency topical steroids (i.e., clobetasol 0.05% cream for body) b.i.d. and oral antihistamines (i.e., cetirizine/loratadine 10 mg/day)	Management: Low- to intermediate-strength topical steroids (i.e., triamcinolone 0.1% cream for body), oral antihistamines (i.e., cetirizine/loratadine 10 mg/day) and oral corticosteroids (i.e., prednisone 0.5–1 mg/kg/day)	Management: High-dose topical corticosteroids (i.e., clobetasol 0.5% cream for body) and oral antihistamines (i.e., cetirizine/loratadine 10 mg/day) while biopsy results pending. Consider adding oral corticosteroids (i.e., prednisone 0.5–1 mg/kg/day or equivalent, followed by rapid taper) if rapidly progressive. Transition to oral doxycycline 100 mg b.i.d. (or tetracycline equivalent) and oral nicotinamide 500 mg b.i.d. after steroid taper, or add to steroid regimen if persistent. Hold immunotherapy. May consider rituximab if refractory
		Continue immunotherapy, but monitor closely for changes in severity. If no or minimal improvement after 2 weeks, reassess and consider referral to dermatology for punch biopsy		
Grade 3	—	Assessment: Same as grade 2 assessment		Assessment: Same as grade 2 assessment
		Management: High-potency topical steroids (i.e., clobetasol 0.05% cream for body) b.i.d. and oral antihistamines (i.e., cetirizine/loratadine 10 mg/day)	Management: Low- to intermediate-strength topical steroids (i.e., triamcinolone 0.1% cream for body), oral antihistamines (i.e., cetirizine/loratadine 10 mg/day) and oral corticosteroids (i.e., prednisone 0.5–1 mg/kg/day)	Management: High-potency topical corticosteroids (i.e., clobetasol 0.5% cream for body) and oral corticosteroids (i.e., prednisone 0.5–1 mg/kg/day or equivalent). Attempt steroid slow taper after 2 weeks. Consider adding oral doxycycline 100 mg b.i.d. (or tetracycline equivalent) and oral nicotinamide 500 mg b.i.d. after steroid taper, or add to steroid regimen if persistent. May consider rituximab if refractory
		Hold immunotherapy until symptoms return to grade 1 severity. Permanently discontinue if recurrence		
Grade 4	—	—	—	Assessment: Hospital admission with dermatology consult. Rule out systemic hypersensitivity syndrome. Laboratory evaluation (CBC with differential, CMP, electrolytes, LFTs). Permanently discontinue immunotherapy. Management: Prednisone 1–2mg/kg (or equivalent dose of IV methylprednisolone) for at least 2 weeks with slow taper. Consider adding oral doxycycline 100 mg b.i.d. (or tetracycline equivalent) and oral nicotinamide 500 mg b.i.d. after steroid taper, or add to steroid regimen if persistent. May consider rituximab if refractory

Note: Recommendations provided are based on case reports, case series, personal experience, and expert consensus.

Abbreviations: —, no data; CBC, complete blood count; CMP, complete metabolic panel; DIF, direct immunofluorescence; HSV, herpes simplex virus; IIF, indirect immunofluorescence; IV, intravenous; LFTs, liver function tests; VZV, varicella zoster virus.

steroids in this population to be ineffective for rapid disease control and prefer upfront combination treatment with high-dose topical corticosteroids and oral steroids. In addition, holding immunotherapy is recommended in patients actively receiving treatment in order to halt further progression of BP. We attempt to rapidly taper patients off of systemic steroids after 2 weeks of treatment; however, this is not always possible, as in the case described here.

Given the numerous side effects associated with prolonged use of systemic steroids, eventual transition to alternative agents is ideal. Although there are limited data to support the use of glucocorticoid-sparing drugs for the treatment of BP, anti-inflammatory and immunosuppressive agents are frequently utilized in clinical dermatology practice. Studies and case reports have demonstrated azathioprine, mycophenolate mofetil, methotrexate, tetracycline antibiotics (i.e., tetracycline, doxycycline, minocycline), dapsone, and nicotinamide to be efficacious steroid-sparing treatments for BP [73–79]. Given the potentially significant toxicity associated with azathioprine, mycophenolate mofetil, and methotrexate in already-immunosuppressed oncologic patients, we prefer use of anti-inflammatory glucocorticoid-sparing agents for the treatment of checkpoint inhibitor-induced BP. Because of their favorable side-effect profile and tolerability, we generally initiate doxycycline and niacinamide immediately before tapering steroids. As in this case, we occasionally add doxycycline and niacinamide to oral and systemic steroid regimens in patients with disease relapse upon steroid taper. In patients with disease refractory to all regimens discussed above, rituximab is a recognized therapy for BP and has been used successfully in one case of nivolumab-induced BP [23].

In general, high-grade dermatologic toxicity secondary to checkpoint inhibitors will require systemic immunosuppression and temporary, if not permanent, cessation of immunotherapy [5, 54, 80, 81]. In patients actively receiving immunotherapy, obtaining disease control as quickly as possible is imperative if treatment is to be reinitiated in a timely manner. Our approach to such patients is outlined in detail in Table 2. Although there is the theoretical concern for reduced efficacy of immunotherapy with concomitant administration of immunosuppressive medications, the available evidence is limited and mixed [82, 83]. As no definitive conclusions can be drawn from existing data regarding cancer outcomes in patients treated with high-dose systemic steroids, we recommend symptomatic treatment of high-grade cutaneous toxicity with systemic immunosuppression. This may facilitate rapid reduction in symptoms and may enable prompt reinitiation of immunotherapy in patients in whom BP can be adequately controlled off systemic steroids.

Conclusion

Cutaneous toxicity is among the most common irAEs associated with checkpoint inhibitor therapy. Although most reactions are mild, some patients may develop severe or life-threatening AEs. Prompt recognition of irAEs is critical in order to prevent and/or reduce interruptions in potentially life-saving cancer therapy. Early treatment of reactions of immune dysregulation is important to limit duration and severity of toxicity. Keeping in mind cutaneous immune-related AEs may have late onset, clinicians should carefully evaluate patients with new skin findings even after their therapy is completed. As PD-1/PD-L1 inhibitors remain relatively new, management of cutaneous toxicity is optimal under multidisciplinary care. Any new symptom should be evaluated and investigated further if not improving.

Author Contributions

Conception/design: Adriana T. Lopez, Larisa Geskin
Provision of study material or patients: Adriana T. Lopez, Larisa Geskin
Collection and/or assembly of data: Adriana T. Lopez, Larisa Geskin
Data analysis and interpretation: Adriana T. Lopez, Larisa Geskin
Manuscript writing: Adriana T. Lopez, Larisa Geskin
Final approval of manuscript: Adriana T. Lopez, Larisa Geskin

Disclosures

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