

Autoimmune Bullous Skin Disorders with Immune Checkpoint Inhibitors Targeting PD-1 and PD-L1

Jarushka Naidoo¹, Katja Schindler², Christiane Querfeld³, Klaus Busam⁴, Jane Cunningham⁵, David B. Page⁶, Michael A. Postow^{7,8}, Alyona Weinstein⁹, Anna Skripnik Lucas⁹, Kathryn T. Ciccolini⁹, Elizabeth A. Quigley^{7,8,10}, Alexander M. Lesokhin^{7,8}, Paul K. Paik^{7,8}, Jamie E. Chaft^{7,8}, Neil H. Segal^{7,8}, Sandra P. D'Angelo^{7,8}, Mark A. Dickson^{7,8}, Jedd D. Wolchok^{7,8,11}, and Mario E. Lacouture^{7,8,10}

Abstract

Monoclonal antibodies (mAb) targeting immune checkpoint pathways such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed death 1 (PD-1) may confer durable disease control in several malignancies. In some patients, immune checkpoint mAbs cause cutaneous immune-related adverse events. Although the most commonly reported cutaneous toxicities are mild, a subset may persist despite therapy and can lead to severe or life-threatening toxicity. Autoimmune blistering disorders are not commonly associated with immune checkpoint mAb therapy. We report a case series of patients who developed bullous pemphigoid (BP), an autoimmune process

classically attributed to pathologic autoantibody formation and complement deposition. Three patients were identified. Two patients developed BP while receiving the anti-PD-1 mAb nivolumab, and one while receiving the anti-PD-L1 mAb durvalumab. The clinicopathologic features of each patient and rash, and corresponding radiologic findings at the development of the rash and after its treatment, are described. Patients receiving an anti-PD-1/PD-L1 mAb may develop immune-related BP. This may be related to both T-cell- and B-cell-mediated responses. Referral to a dermatologist for accurate diagnosis and management is recommended. *Cancer Immunol Res*; 4(5); 383–9. ©2016 AACR.

Background

Immune checkpoint monoclonal antibodies (mAb) that block cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed death 1 (PD-1), and programmed death ligand 1 (PD-L1) may generate durable antitumor responses in a number of malignancies (1–3). Side effects of these agents may be attrib-

uted to a persistently stimulated immune system and are thus termed "immune-related adverse events" (irAE). The precise mechanisms underlying the development of irAEs are not fully understood, but are postulated to be largely T-cell mediated (4). Examples of such toxicities include colitis, hepatitis, thyroiditis, pneumonitis, and hypophysitis. Specific target antigens that may underlie the development of these toxicities are not yet known.

The incidence of skin rash as a result of anti-CTLA-4 and anti-PD-1 therapy is over 20%, with a higher reported incidence with anti-CTLA-4 mAb (3, 5). The most common cutaneous irAE is a generalized maculopapular eruption. Pathologic features of this rash include perivascular eosinophilic and leukocytic infiltrates (6), and may be associated with peripheral eosinophilia (7). Although cutaneous irAEs are usually mild to moderate in severity, severe reactions have been reported, including toxic epidermal necrolysis (TEN), Stevens–Johnson syndrome (SJS), and vasculitis or drug reaction with eosinophilia and systemic symptoms (DRESS), as a result of ipilimumab treatment (6, 8, 9). These reactions, although potentially life-threatening, are usually reversible upon discontinuation of the mAb and with systemic treatment. Blistering skin disorders are not commonly associated with immune checkpoint mAb therapy. One case of bullous pemphigoid (BP) secondary to the anti-PD-1 agent pembrolizumab has been reported in a patient with metastatic melanoma (10). The underlying mechanisms for the development of this toxicity and standard approaches for its diagnosis and management in patients receiving immune checkpoint mAbs have not been described.

Standard diagnostic workup for blistering disorders comprises dermatologic referral and a skin biopsy of lesional and

¹Department of Oncology, Sidney Kimmel Cancer Center at Johns Hopkins, Baltimore, Maryland. ²Department of Dermatology and Dermato-oncology, Medical University of Vienna, Vienna General Hospital, Vienna, Austria. ³Department of Dermatology and Dermato-pathology, City of Hope Cancer Center and Beckman Research Institute, Duarte, California. ⁴Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, New York. ⁵Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, New York. ⁶Department of Medicine, Portland Providence Medical Center, Earl A. Chiles Research Institute, Portland, Oregon. ⁷Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York. ⁸Weill Cornell Medical College, New York, New York. ⁹Department of Nursing, Memorial Sloan Kettering Cancer Center, New York, New York. ¹⁰Department of Dermatology, Memorial Sloan Kettering Cancer Center, New York, New York. ¹¹Ludwig Center for Cancer Immunotherapy, Memorial Sloan Kettering Cancer Center, New York, New York.

Note: Current address for J. Naidoo: Sidney Kimmel Cancer Center at Johns Hopkins Department of Oncology, Upper Aerodigestive Division, Baltimore, Maryland.

J. Naidoo and K. Schindler contributed equally to this article.

Corresponding Author: Jarushka Naidoo, Johns Hopkins Bayview, 4940 Eastern Avenue, Baltimore, MD 21224; Phone: 410-550-2646; Fax: 410-550-5445; E-mail: jnaidoo1@jhmi.edu

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perilesional tissue, to initially establish whether the abnormality is intraepidermal or subepidermal by hematoxylin and eosin staining. This is followed by further assessments, including direct immunofluorescence (DIF), indirect immunofluorescence (IIF) using monkey esophagus, and serologic testing for circulating or tissue-bound autoantibodies by ELISA (11). BP is the most common blistering skin disorder; the pathognomonic features seen with DIF include a subepidermal cleft and linear deposits of IgG and C3 at the blister roof at the dermoepidermal junction, and a band-like pattern at the dermoepidermal junction on IIF using monkey esophagus (11). Other subepidermal blistering disorders are ruled out in order to establish a diagnosis of BP, including epidermolysis bullosa acquisita (EBA), which has positive DIF staining of the blister floor. Patients who develop BP normally present with an initial nonbullous phase of pruritus, followed by development of generalized or localized tense blisters filled with serous or hemorrhagic fluid, and 10% to 30% of cases show involvement of the oral mucosa (11, 12). Implicated antigenic targets for BP include the hemidesmosomal structural proteins of the dermoepidermal junction, BP180 (collagen XVII), and BP230 (13). Serologic testing by ELISA for circulating autoantibodies against BP180 and BP230 may be used to confirm the diagnosis, correlate with disease severity, or monitor response to treatment (13, 14). Whereas classic BP is idiopathic, more than 50 medications are associated with drug-induced BP, including antibiotics, nonsteroidal anti-inflammatory drugs, diuretics, oral hypoglycemic agents, anti-hypertensives, and others (15, 16). No specific features differentiate classic BP from drug-induced BP. Drug-induced BP usually resolves after withdrawal of the causative agent, but may follow a chronic course resembling classic BP (15). The underlying mechanisms for drug-induced BP are unclear.

Herein, we describe the diagnosis, management, and outcomes of three patients who developed BP while receiving anti-PD-1/PD-L1 immune checkpoint mAbs. In addition, we hypothesize that blockade of the PD-1/PD-L1 pathway may increase autoantibody production against the hemidesmosomal protein BP180, through a process that is both T-cell and B-cell mediated. We also hypothesize that this mechanism may contribute to achieving an antitumor response with PD-1/PD-L1 mAbs, as melanoma, non-small cell lung carcinomas (NSCLC), and the basement membrane of the skin can express BP180 as a common antigen (17, 18). Autoimmune blistering disorders have not been observed with anti-CTLA-4 therapy to our knowledge; we thus propose that BP may be a class effect of anti-PD-1/PD-L1 therapy.

Case Series

Case 1

An 80-year-old man with metastatic melanoma, previously treated with ipilimumab (3 mg/kg) every 3 weeks for 4 cycles of therapy that was complicated by mild pruritus, was treated with second-line nivolumab (3 mg/kg) every 2 weeks. After 10 doses, the patient developed pruritus and a faint maculopapular rash. One month later, he developed tense bullae (Fig. 1A) without mucosal involvement. The patient had no underlying skin or autoimmune disorders, no recent exposure to light or radiation, and no new medications. Comprehensive diagnostic workup for a blistering disorder was performed, including DIF, IIF, BP ELISA, and salt-split skin analysis to rule out EBA. The histopathology review showed an ulcerated and inflamed subepidermal vesicular dermatitis with eosinophils (Fig. 1B), DIF revealed linear disposition of C3 and

IgG at the basal membrane zone (Fig. 1C), IIF on monkey esophagus was positive (IgG 40, IgG4:160), and salt-split skin analysis revealed IgG at the epidermal side of the blister, consistent with BP. At the time of the development of the rash, a mildly elevated peripheral eosinophilia of 13.5% was noted on evaluation of the complete blood count, suggestive of BP. From a therapeutic perspective, the patient experienced a near-complete response to nivolumab (Fig. 1D and F) and continued on this therapy with close dermatologic monitoring. He experienced ongoing pruritus and developed urticarial lesions and bullae. His symptoms peaked after each dose of anti-PD-1 therapy, and he was treated with topical steroids (clobetasol spray 0.05%, twice daily; betamethasone cream 0.1%, between treatments), antihistamines (hydroxyzine, 25 mg nightly), and intermittent oral steroids (prednisone, 20 mg tapered over 2 weeks; nicotinamide, 500 mg four times daily; clobetasol, 0.05% topical, twice daily to active lesions only) according to severity. BP ELISA was analyzed on two separate occasions during treatment with systemic corticosteroids and was positive (Table 1). After 26 doses of nivolumab (3 mg/kg), the patient began to develop erosions and vesicles on the buccal mucosa. These were treated with oral tacrolimus ointment (0.1% ointment, two to four times daily) and dexamethasone swish/spit. The patient's nivolumab was then withheld. Over the next 4 months and at the time of this report, the patient had been treated with nicotinamide and a short course of antibiotic therapy (tetracycline, 500 mg four times daily; ofloxacin, 0.3% drops daily; mupirocin ointment to crusted lesions; clindamycin 1% lotion, twice daily to face) for superimposed skin infection. The severity of the rash ranged from grades 1 to 2 during the patient's clinical course. The patient's melanoma remains in complete remission now 5 months after the administration of the last dose of nivolumab.

Case 2

A 78-year-old woman with metastatic melanoma was treated with durvalumab (1 mg/kg every 2 weeks) as second-line therapy, after first-line ipilimumab (3 mg/kg) every 3 weeks for 4 cycles of therapy without associated irAEs. The patient had no relevant history of skin or autoimmune disorders or recent exposure to light or radiation, and no new medications. After 8 doses of durvalumab, the patient developed a maculopapular rash on her back, which was managed successfully with topical steroids (tacrolimus 0.1% ointment, 2–4 times daily). After an additional 4 doses of anti-PD-L1 therapy, a biopsy of the rash showed pauci-inflammatory lichenoid dermatitis, suggesting a drug reaction. Subsequently, after almost 1 year of durvalumab therapy, she developed two fluid-filled, pruritic, tense blisters on the dorsum of her foot (Fig. 2A), accompanied by a new, intensely pruritic rash involving her torso and extremities. In light of these findings, subsequent dosing was withheld. A skin biopsy of the new blistering rash revealed a subepidermal cleft (Fig. 2B) with deposition of IgG and C3 on DIF (Fig. 2C), positive IIF on monkey esophagus (IgG 320, IgG4:160), negative salt-split skin analysis, and elevated BP180 (72.0) and BP230 (21.7) titers on serum ELISA while she was receiving topical steroid therapy (Table 1). The patient then developed buccal mucosal involvement and her rash evolved from erythematous patches into tense discrete bullae. At the time of initial development of the rash, her eosinophil count increased compared with pretreatment levels but remained within normal range. Her skin condition improved slightly with topical steroids alone (clobetasol solution 0.05%, two to four times daily). The severity of the patient's rash ranged from grades 1 to 2. The patient showed a partial response to therapy by radiologic assessment at the time of

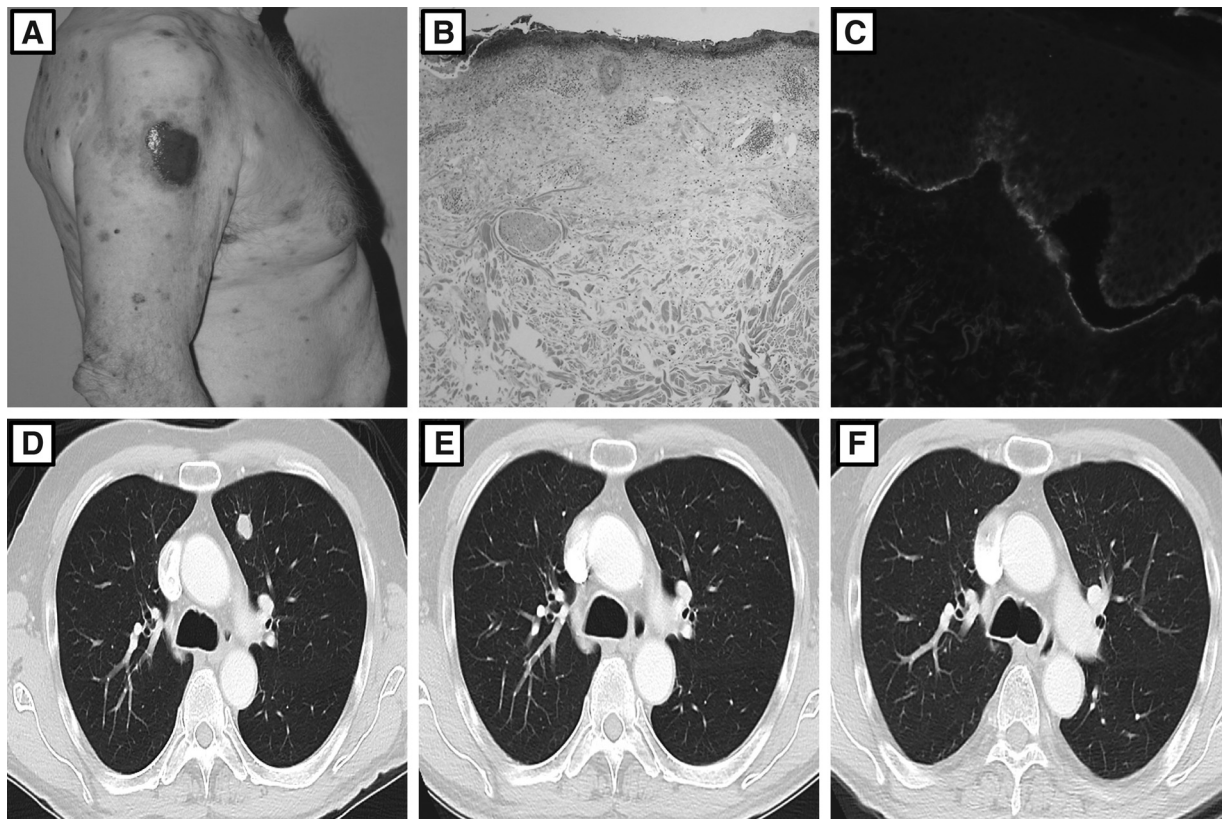


Figure 1. Clinico-pathologic features and serial radiologic imaging of case 1. A, clinical presentation: multiple excoriating blisters on the trunk; B, hematoxylin and eosin histopathologic slide, demonstrating subepidermal cleft and eosinophilic infiltrate; C, direct immunofluorescence demonstrating IgG positivity at the dermoepidermal junction; D, baseline CT scan image before treatment with immune checkpoint therapy, demonstrating lung metastasis; E, CT scan image at the time of development of bullous pemphigoid, demonstrating partial radiologic response; F, CT scan image 6 months after the diagnosis of bullous pemphigoid, demonstrating ongoing partial response.

development of BP, which is ongoing, 1 year after discontinuation of therapy (Fig. 2D and F). She continues to develop intermittent isolated pruritic lesions on her trunk, which are treated effectively with topical steroids (clobetasol solution 0.05% as required).

Case 3

An 85-year-old man with metastatic squamous cell carcinoma of the lung with progressive disease following 6 cycles of first-line

platinum doublet chemotherapy (carboplatin, AUC = 5; paclitaxel, 175 mg/m² i.v. every 3 weeks) was treated with nivolumab (3 mg/kg) every 2 weeks. After 3 months of therapy, the patient developed a pruritic, maculopapular, and erythematous rash. The patient had no history of underlying skin or autoimmune disorders, no recent exposure to light or radiation, and no new medications. Histopathologic evaluation of the rash showed a spongiotic, vesicular, and superficial perivascular dermatitis

Table 1. Patient demographics and diagnostic workup

Age (y)	Sex	Tumor type	Current therapy	Prior therapies	DIF	IIF	Salt-split skin analysis	Time of rash onset (from start of therapy)	BP ELISA titers (from time taken since start of therapy)
80	Male	Melanoma	Nivolumab	Ipilimumab	+	+	+	24 weeks	At 33.9 weeks: BP180: 13.8* BP230: 10.0* At 47.0 weeks: BP180: 25.6* BP230: 12.2*
78	Female	Melanoma	Durvalumab	Ipilimumab	+	+	+	17.9 weeks	At 44.1 weeks: BP180: 72* BP230: 21.7*
85	Male	Non-small cell lung cancer	Nivolumab	Carboplatin + paclitaxel	+	NA	NA	6.1 weeks	At 55.1 weeks: BP180: 1.1* BP230: 0.9*

Abbreviations: DIF, direct immunofluorescence; IIF, immunofixation; NA, not applicable (not completed). *BP ELISA taken during steroid therapy.

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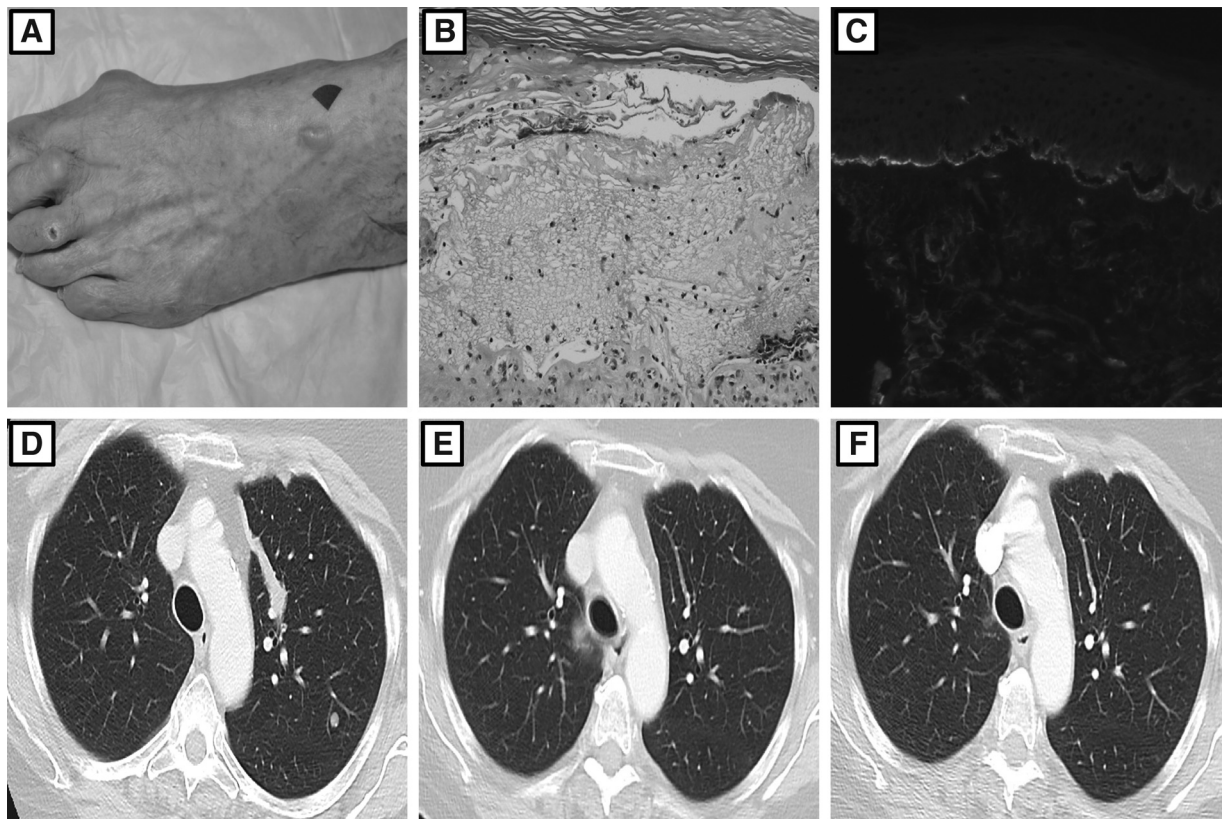


Figure 2.

Clinicopathologic features and serial radiologic imaging of case 2. A, clinical presentation: tense blister on the dorsum of the left foot; B, hematoxylin and eosin histopathologic slide, demonstrating subepidermal cleft and eosinophilic infiltrate; C, direct immunofluorescence demonstrating subepidermal cleft and C3 deposition at the dermoepidermal junction; D, baseline CT scan image prior to treatment with immune checkpoint therapy, demonstrating lung metastasis; E, CT scan image at the time of diagnosis of bullous pemphigoid, demonstrating partial response; F, CT scan image 12 months after discontinuation of treatment, demonstrating no evidence of disease.

thought to represent drug-induced hypersensitivity. The rash improved with topical high-potency steroids (clobetasol 0.05%, two to four times daily). However, after the patient's ninth dose of nivolumab, he developed small cutaneous vesicles and bullae, which progressed to involve more than 30% of his body surface, consistent with a grade 3 rash (Fig. 3A). His nivolumab therapy was subsequently discontinued. A repeat skin biopsy revealed a subepidermal bullous dermatitis with eosinophils (Fig. 3B). Blood eosinophils increased compared with pretreatment and peaked at the time of diagnosis of BP, but remained within normal limits. DIF revealed linear deposition of IgG and C3 at the basement membrane zone of the dermoepidermal junction, consistent with BP (Fig. 3C). BP180 and BP230 autoantibodies were negative; however, these were tested after initiation and while the patient was receiving oral steroids. The cutaneous eruption remained stable with oral steroid therapy, dosed according to severity. The patient continued to develop new BP lesions after discontinuation of nivolumab for over 10 months. He was subsequently tapered off oral prednisone (prednisone, 40 mg tapered over 12–13 weeks; followed by methylprednisone, 20 mg 2 months later; tapered over 3 weeks; followed by prednisone taper over 2 weeks) and treated with intermittent topical steroids (clobetasol cream 0.05% twice daily). The patient's squamous cell lung cancer has been stable on restaging CT scans since commencement of therapy and

remains stable 15 months after the patient's last dose was administered (Fig. 3D and F).

Discussion

These cases illustrate the diagnosis, management, and antitumor response seen in three patients who developed BP while receiving nivolumab and durvalumab, respectively. In the context of one previous case report describing this phenomenon with pembrolizumab (10), we hypothesize that this clinical manifestation is likely to represent a class effect of these agents.

These cases display characteristics of both classic and drug-induced BP. Diagnostic tests for BP were positive in all three cases discussed above, after early referral to a dermatologist and diagnostic workup. Their clinical courses were distinct from traditional drug-induced BP, which usually resolves abruptly upon withdrawal of the causative agent (16). BP associated with anti-PD-1/PD-L1 mAbs may persist for several months after discontinuation of the agent. This could be explained by the continued *in vivo* effect of immune checkpoint mAbs, which persists regardless of discontinued dosing, due to continued immune activation (3). This possibility is also supported by the fact that all three patients had continued antitumor response or stable disease, in addition to continued blistering. These observations will need additional

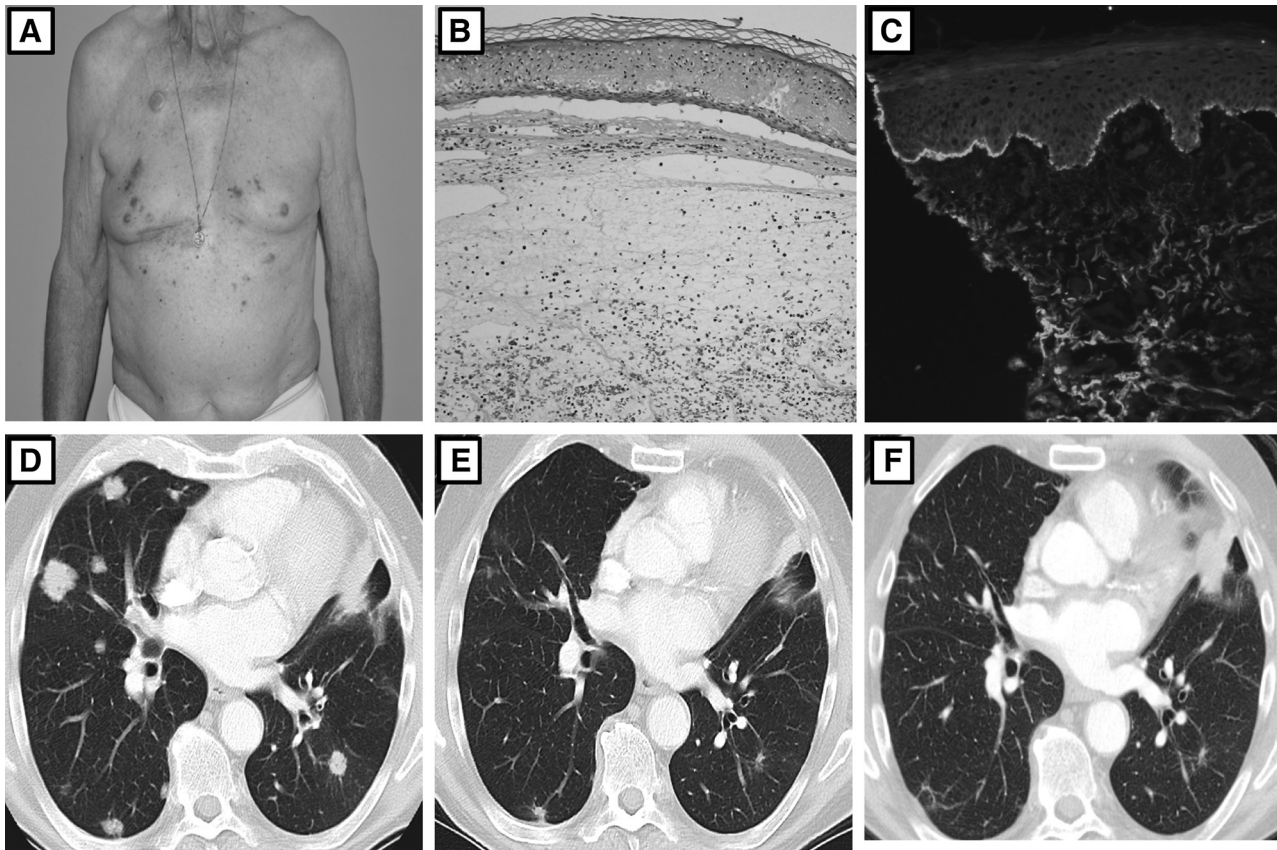


Figure 3.

Clinicopathologic features and serial radiologic imaging of case 3. A, clinical presentation: multiple papules and blisters on the trunk; B, hematoxylin and eosin histopathologic slide, demonstrating subepidermal cleft and eosinophilic infiltrate; C, direct immunofluorescence demonstrating subepidermal cleft and C3 deposition at the dermoepidermal junction; D, baseline CT scan image prior to treatment with immune checkpoint therapy, demonstrating lung metastases; E, CT scan image at the time of diagnosis of bullous pemphigoid, demonstrating partial response; F, CT scan image 12 months after discontinuation of immune checkpoint therapy, demonstrating ongoing partial response.

investigation to confirm a relationship between both findings. In case 1, cutaneous symptoms peaked after each dose of treatment, suggesting BP flare due to repeated dosing. In cases 2 and 3, patients exhibited ongoing cutaneous eruptions despite cessation of the offending agent. Thus, although continued dosing may worsen BP, discontinuing the offending agent may not lead to complete resolution, and these patients may require intermittent or ongoing BP treatment.

BP with anti-PD-1/PD-L1 mAbs may occur within several months after initiation of the offending agent and may be accompanied or preceded by pruritus. In the patients described, the onset of pruritus occurred within the first 3 to 4 months of initiation of anti-PD-1/PD-L1 therapy. Pruritus in the setting of mAb therapy is a common clinical finding; however, patients who manifest this symptom could represent a subset of patients with a nonbullous form of BP. Circulating autoantibodies against BP180 may be present prior to the development of blisters or during the pruritic phase. Thus, in patients with persistent or unusual pruritus, dermatologic evaluation for potential subclinical BP may be considered.

In terms of treatment, topical and systemic steroids were administered according to severity. In a comparison of oral and topical steroid therapy in patients with moderate to severe BP of classic type, topical steroid treatment with clobetasol was superior to systemic treatment with prednisone (1 mg/kg/day),

with regard to BP control, occurrence of side effects, and duration of hospitalization (19). In the above reported cases, the patients were successfully managed mainly with topical steroids.

Why some patients develop immune-related BP and others do not is currently unclear; however, this could be related to the possession of a common target antigen located both at the dermoepidermal junction and on tumor cells. BP180 is an antigen that can be expressed on the surface of malignant melanocytic tumor cells, NSCLC cells, and the basement membrane of the skin (17, 18). Thus, it is possible that this phenomenon is mediated by T cells targeting BP180 on tumor cells, as well as the basement membrane of the skin. Since BP180 is also expressed in other tissues, it is possible that other irAEs may develop as a result of a similar underlying mechanism involving autoantibody production (20). In our series, two of three cases had elevated serum BP180 and BP230 autoantibodies; however, one of these patients had testing while receiving systemic steroids, and no patient had autoantibody titers assessed both before and after therapy, which limits our ability to draw strong conclusions from this observation. From here, we plan to assess the primary and metastatic tumor tissue of the three patients in this case series for expression of BP180 using immunohistochemistry in an attempt to demonstrate a potential on-target effect. Future studies may be done to assess BP180 and BP230 levels before and after steroid

therapy in patients who develop BP in the context of anti-PD-1/PD-L1 therapy.

A number of theories have been proposed to explain the immunologic mechanism of BP. In a mouse model, antibodies to BP180 were pathogenic, and depletion of complement, neutrophils, or mast cells abrogated the pathogenic effect of the BP180 antibodies, thus highlighting the role of the innate immune system in BP (21). The role of T cells in the pathogenesis of BP remains unclear. In drug-induced BP, it has been postulated that exposure to certain drugs may lead to depletion of CD4⁺CD25⁺Foxp3⁺ regulatory T cells, which can in turn lead to proliferation of autoantibody-secreting B-cell clones (22). In the context of PD-1/PD-L1 blockade, the principal effect of blocking this axis is the reinvigoration of exhausted T cells (23). It has also been postulated that anti-PD-1/PD-L1 therapy leads to an interaction between PD-1/PD-L1 expressing B cells and PD-1⁺ follicular helper T cells, thus facilitating a B-cell germinal center response that favors a humoral rather than a cellular response (24, 25). Although a similar interaction and clinical cases of BP have not been described to our knowledge in the context of CTLA-4 blockade, further studies are required to determine whether BP may develop with mAbs to CTLA-4.

Conclusions

Clinicians prescribing anti-PD-1/PD-L1 therapy should be aware of the clinical manifestations of BP and recognize that this may be a class effect of these agents. We recommend that if BP is suspected, clinicians refer patients to a dermatologist for early evaluation and institute topical or systemic immunosuppressive therapy when necessary. Discontinuation of anti-PD-1/PD-L1 therapy may be required. Dermatologic evaluation should also be considered in patients experiencing persistent pruritus to evaluate for the non-bullous variant of BP. The mechanisms underlying the development of irAEs with immune checkpoint mAbs warrant further investigation. Although autoimmune phenomena caused by immune checkpoint mAbs are assumed to be T cell mediated, B cells and the innate immune system may be closely interlinked and could play a crucial role in the development of irAEs. Dermatologic manifestations like BP may be instructive, in that they may identify potential target antigens and stimulate further study of the mechanisms underlying irAEs.

Disclosure of Potential Conflicts of Interest

M.A. Postow reports receiving commercial research support from Bristol Myers-Squibb and is a consultant/advisory board member for Bristol Myers-

Squibb and Amgen. A. Weinstein reports serving as a consultant for Bristol Myers-Squibb. K.T. Ciccolini is a consultant/advisory board member for EAISI and has provided expert testimony for Amgen, Physician Education Resource, Dermatology Nurses Association, Oncology Nursing Society, and Clinical Assistance Programs LLC. A.M. Lesokhin reports receiving commercial research support from Bristol Myers-Squibb and is a consultant/advisory board member for the same. J.E. Chaff reports serving as a consultant/advisory board member for Genentech. N.H. Segal reports receiving commercial research support from Bristol-Myers Squibb, AstraZeneca/MedImmune, Roche/Genentech, and Merck, and is a consultant/advisory board member for Bristol-Myers Squibb, AstraZeneca/MedImmune, Roche/Genentech, and Pfizer. J.D. Wolchok reports receiving commercial research support from Bristol-Myers Squibb and is a consultant/advisory board member for Bristol-Myers Squibb, Merck, Medimmune, and Genentech. M.E. Lacouture reports receiving commercial research support from Berg, Bristol-Myers Squibb, and Genentech and is a consultant/advisory board member for Roche, Genentech, Bristol-Myers Squibb, Merck, and Novartis. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: J. Naidoo, K. Schindler, C. Querfeld, K. Busam, J.E. Chaff, M.A. Dickson, J.D. Wolchok, M.E. Lacouture

Development of methodology: J. Naidoo, K. Schindler, J.D. Wolchok, M.E. Lacouture

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J. Naidoo, K. Schindler, C. Querfeld, K. Busam, J. Cunningham, A. Weinstein, A.S. Lucas, E.A. Quigley, A.M. Lesokhin, P.K. Paik, J.E. Chaff, N.H. Segal, S.P. D'Angelo, M. Dickson, J.D. Wolchok, M.E. Lacouture

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J. Naidoo, K. Schindler, C. Querfeld, K. Busam, J. Cunningham, D.B. Page, J.E. Chaff, M.A. Dickson, J.D. Wolchok, M.E. Lacouture

Writing, review, and/or revision of the manuscript: J. Naidoo, K. Schindler, C. Querfeld, K. Busam, J. Cunningham, D.B. Page, M.A. Postow, A. Weinstein, A.S. Lucas, K.T. Ciccolini, E.A. Quigley, A.M. Lesokhin, P.K. Paik, J.E. Chaff, N.H. Segal, S.P. D'Angelo, M. Dickson, J.D. Wolchok, M.E. Lacouture

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J. Naidoo, J. Cunningham, M.E. Lacouture

Study supervision: J. Naidoo, K. Busam, S.P. D'Angelo, J.D. Wolchok, M.E. Lacouture

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