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Risk Factors for the Development of Bullous Pemphigoid in US Patients Receiving Immune Checkpoint Inhibitors

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IMPORTANCE De novo bullous pemphigoid (BP) is a rare immune-mediated adverse event from immune checkpoint inhibitors (ICIs) that can necessitate permanent discontinuation of the anticancer therapy, but the risk factors for developing this toxic effect are unknown.

OBJECTIVE To compare potential risk factors for BP in patients treated with ICIs who did and did not develop BP.

DESIGN, SETTING, AND PARTICIPANTS This cohort and nested propensity score–matched case-control study was conducted at the Dana-Farber Cancer Institute, Brigham and Women's Hospital, and Massachusetts General Hospital. All patients at these facilities with de novo BP after ICI treatment were compared with all patients on the cancer registry who were treated with ICIs between October 1, 2014, and December 31, 2020. Patients with incomplete or blinded data regarding the ICI agent or total cycles were excluded.

EXPOSURES In the cohort, assessed potential risk factors included age at ICI introduction, sex, ICI molecular target, and cancer type, which were then used as matching variables. In the propensity score–matched case-control analysis, risk factors assessed included sex, race and ethnicity, cancer stage, metastasis sites, idiopathic BP comorbidities, pre–ICI vaccination, radiation history, body mass index, and derived neutrophil-to-lymphocyte ratio.

MAIN OUTCOMES AND MEASURES Diagnosis of BP at any point after ICI treatment, confirmed by direct immunofluorescence, indirect immunofluorescence, autoantibody serologies, or diagnostic consensus among study board-certified dermatologists. Odds ratios (ORs) and 95% CIs were calculated for all risk factors. In the secondary analysis, best overall responses to ICIs between cases and controls were compared by Fisher exact test.

RESULTS Among 5636 patients treated with ICIs at Dana-Farber Cancer Institute, Brigham and Women's Hospital, and Massachusetts General Hospital during the study period, 35 (0.6%; median [IQR] age, 72.8 [13.4] years; 71.4% [25] male patients) developed BP. In a multivariate logistic regression model that assessed 2955 patients with complete data in the cancer registry, age 70 years or older (OR, 2.32; 95% CI, 1.19-4.59; $P = .01$), having melanoma (OR, 3.21; 95% CI, 1.51-6.58; $P < .003$), and having nonmelanoma skin cancer (OR, 8.32; 95% CI, 2.81-21.13; $P < .001$) were significantly associated with developing BP. In the nested 1:2 case-control comparison of all 35 cases to 70 propensity score–matched controls, a complete or partial response on initial restaging imaging was a risk factor for BP development (OR, 3.37; 95% CI, 1.35-9.30; $P = .01$). Bullous pemphigoid cases also more frequently exhibited overall tumor response to ICIs than matched controls (29 of 35 [82.9%] vs 43 of 70 [61.4%]; $P = .03$).

CONCLUSIONS AND RELEVANCE In this cohort study, age 70 years or older and skin cancer were associated with increased risk of developing ICI-associated BP. Given the association of BP with improved initial and best overall tumor responses, early identification and toxic effect–directed treatment should be prioritized, especially in individuals at risk for developing de novo BP.

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Supplemental content

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Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of late-stage and metastatic cancers.[1] These agents target the immune cell surface proteins programmed cell death 1 protein (PD-1), programmed cell death 1 ligand 1, and cytotoxic T-lymphocyte-associated protein 4, upregulating the endogenous cytotoxic T-cell-associated antitumor immune response.[1] Immune checkpoint inhibitor therapy is frequently complicated by heterogeneous immune-related adverse events, which occur in the skin in 30% to 50% of treated patients.[1] Despite its primarily B-cell-mediated pathophysiology, bullous pemphigoid (BP) is a rare but often severe dermatologic adverse event, frequently necessitating systemic immunosuppression and permanent ICI discontinuation.[2-4]

Reported risk factors for idiopathic BP include advanced age (particularly age 70 years or older), dipeptidyl peptidase-4 inhibitors, type 2 diabetes, cerebrovascular disease, and neurocognitive disease.[5-7] In contrast, the risk factors for developing dermatologic adverse events among patients treated with ICIs are less well understood. Previous studies have suggested that elevated body mass index, derived neutrophil-to-lymphocyte ratio greater than 3, combination anti-PD-1 and cytotoxic T-lymphocyte-associated protein 4 inhibitor regimens, melanoma, and renal cell carcinoma may be risk factors for dermatologic adverse event development.[8-10] However, research identifying risk factors for specific dermatologic adverse event phenotypes—such as BP—is lacking.

Identifying risk factors for developing BP is important to oncologists and dermatologists given that this toxic effect is associated with improved tumor responses but can ultimately adversely affect sustained ICI delivery.[2] To address this knowledge gap, we performed a case-control study nested within a large multi-institutional retrospective cohort study to identify risk factors for ICI-induced BP.

Key Points

Question What risk factors are associated with development of bullous pemphigoid (BP) in patients receiving immune checkpoint inhibitors (ICIs)?

Finding In this cohort study of 2955 patients treated with ICIs, age 70 years or older or having melanoma or nonmelanoma skin cancer was associated with elevated risk for developing ICI-induced BP.

Meaning Patients with risk factors for BP development should be counseled and monitored throughout ICI treatment.

Methods

In this cohort study, the Dana-Farber Cancer Institute, Brigham and Women's Hospital, and Massachusetts General Hospital patient registries were identically queried to identify ICI-induced BP cases from October 1, 2014, to December 31, 2020, confirmed by consensus among study dermatologists. Separately, all patients in the Dana-Farber Cancer Institute cancer registry who received ICIs in the study period were identified as controls. Age at ICI initiation, sex, ICI agents, and cancer type were collected from the cancer registry as preselected potential risk factors. Age was categorized as younger than 70 years or 70 years or older. Immune checkpoint inhibitors were collapsed by molecular target. Patients who received ICIs in double-blinded clinical trials or with incomplete data were excluded. Given the rarity of ICI-induced BP, Firth bias-reduced penalized-likelihood logistic regression models were fit for univariate and multivariate analysis. The Dunnett correction was adjusted for multiple comparisons to identical reference groups for cancer type. This study was approved by the Mass General Brigham Institutional Review Board, which waived the informed consent requirement because only deidentified data were used. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Propensity score matching was completed based on age, cancer type, ICI agent, and ICI cycles received to select 2 controls per case before medical record review. The number of received ICI cycles was included to control for guarantee-time bias; cycle number was categorized per 5 cycles. Medical records were reviewed for the following preselected potential ICI-induced BP risk factors: sex, race and ethnicity, cancer stage, metastatic sites, BP-associated diseases, vaccination in 6 months before ICI, radiation history, and both initial and best overall tumor responses. Race and ethnicity were abstracted exactly as it was recorded in the medical record. We categorized patients as having White or other (Asian and Pacific Islander, Hispanic or Latino, or unspecified race and ethnicity) race and ethnicity given that our institution's patient population is predominantly of White race and was assumed to be underpowered to evaluate individuals of other races and ethnicities. Tumor response was categorized using Response Evaluation Criteria in Solid Tumors 1.1, per oncologist assessment on initial restaging. Body mass index (calculated as weight in kilograms divided by height in meters squared) was abstracted from within 6 months of ICI initiation. The derived neutrophil-to-lymphocyte ratio was abstracted from a differentiated complete blood count on the day of ICI initiation. Odds ratios (ORs) and 95% CIs were calculated for all risk factors. In the secondary analysis, best overall tumor responses were compared by Fisher exact test between cases and all controls as well as between cases and controls lacking dermatologic adverse events given potential confounding of dermatologic adverse events with tumor response. R software, version 4.0.3 (R Foundation for Statistical Computing) was used to analyze the data. The threshold for statistical significance was 2-sided $P \leq .05$.

Results

Among 5636 patients treated with ICIs in the study period (October 1, 2014, to December 31, 2020), 35 (0.6%) developed BP. These 35 patients (median [IQR] age, 72.8 [13.4] years; 71.4% [25] male and 28.6% [10] female patients) were compared with all patients treated with ICIs included in the cancer registry with complete data and who did not develop BP (2920; median [IQR] age, 65.5 [15.72] years; 55.0% [1607] male and 45.0% [1313] female patients) (**Table 1**).

Table 1. Descriptive Statistics of Patient Characteristics and Univariate Logistic Regression

Characteristic	All patients, No. (%) (n = 2955)	BP status, No. (%)		Firth bias-reduced penalized-likelihood logistic regression	
		No BP (n = 2920)	BP (n = 35)	OR (95% CI)	Univariate *P* value
Age at first ICI cycle, y					
<70	1892 (64.0)	1877 (64.3)	15 (42.9)	1 [Reference]	.01
≥70	1063 (36.0)	1043 (35.7)	20 (57.1)	2.38 (1.23-4.70)	
Sex					
Male	1632 (55.2)	1607 (55.0)	25 (71.4)	1.98 (0.99-4.27)	.05
Female	1323 (44.8)	1313 (45.0)	10 (28.6)	1 [Reference]	
ICI agent					
Atezolizumab	153 (5.2)	153 (5.2)	0	NA	NA[a]
Avelumab	17 (0.6)	17 (0.6)	0		
Cemiplimab	22 (0.7)	22 (0.8)	0		
Durvalumab	78 (2.6)	78 (2.7)	0		
Ipilimumab	35 (1.2)	35 (1.2)	0		
Nivolumab	1055 (35.7)	1041 (35.7)	14 (40.0)		
Nivolumab + ipilimumab	190 (6.4)	188 (6.4)	2 (5.7)		
Pembrolizumab	1405 (47.5)	1386 (47.5)	19 (54.3)		
Immunotherapy type					
CTLA-4	35 (1.2)	35 (1.2)	0	1 [Reference]	.30[a]
PD-1	2482 (84.0)	2449 (83.9)	33 (94.3)	0.97 (0.13-123.78)	
PD-1 and CTLA-4	190 (6.4)	188 (6.4)	2 (5.7)	0.94 (0.07-130.95)	
PD-L1	248 (8.4)	248 (8.5)	0	0.14 (0-26.55)	
Cancer type (organ)					
Nonskin cancer[b,c]	2375 (80.4)	2357 (80.7)	18 (51.4)	1 [Reference]	<.01
Melanoma	505 (17.1)	493 (16.9)	12 (34.3)	3.23 (1.53-6.60)	
Nonmelanoma skin cancer[d,e]	75 (2.5)	70 (2.4)	5 (14.3)	9.94 (3.38-24.98)	
Epithelial tumor origin					
Epithelial tumors	2836 (96.0)	2801 (95.9)	35 (100)	1 [Reference]	.35
Nonepithelial tumors[f]	119 (4.0)	119 (4.1)	0	0.33 (0-2.35)	

Abbreviations: BP, bullous pemphigoid; CTLA-4, cytotoxic T-lymphocyte–associated protein 4; ICI, immune checkpoint inhibitor; NA, not applicable; OR, odds ratio; PD-1, programmed cell death 1 protein; PD-L1, programmed cell death 1 ligand 1.

[a] Given the large number of ICI agent groups, the *P* value for ICI agent was calculated among pooled groups by molecular target.

[b] Nonskin cancers in the no BP group that made up greater than 1.0% of the total sample (2357) included lung cancer (1218 [51.7%]), renal cancer (219 [9.3%]), bladder or urothelial cancer (193 [8.2%]), head and neck carcinomas (177 [7.5%]), gastrointestinal malignant tumors (155 [6.6%]), brain or central nervous system tumors (74 [3.1%]), lymphoma in lymph nodes (50 [2.1%]), breast cancer (46 [2.0%]), liver cancer (44 [1.9%]), and cervical or uterine carcinoma (38 [1.6%]).

[c] Nonskin cancers in the BP group (18) included lung cancer (8 [44.4%]), renal cancer (3 [16.7%]), bladder or urothelial cancer (2 [11.1%]), esophageal cancer (1 [5.6%]), prostate cancer (1 [5.6%]), colon cancer (1 [5.6%]), breast cancer (1 [5.6%]), and salivary gland cancer (1 [5.6%]).

[d] Nonmelanoma skin cancers in the no BP group (70) included Merkel cell carcinoma (35 [50.0%]), squamous cell carcinoma (34 [48.6%]), and basal cell carcinoma (1 [1.4%]).

[e] Nonmelanoma skin cancers in the BP group (35) included squamous cell carcinoma (4 [11.4%]) and basal cell carcinoma (1 [2.9%]).

[f] Nonepithelial tumors in the no BP group (119) included diffuse large B-cell lymphoma (36 [30.3%]), Hodgkin lymphoma (27 [22.7%]), acute myeloid leukemia (8 [6.7%]), chronic lymphocytic leukemia (6 [5.0%]), leiomyosarcoma (5 [4.2%]), B-cell lymphoma, not otherwise specified (4 [3.4%]), multiple myeloma (4 [3.4%]), follicular lymphoma (3 [2.5%]), liposarcoma (3 [2.5%]), lymphoma, not otherwise specified (3 [2.5%]), sarcoma, not otherwise specified (3 [2.5%]), angiosarcoma (2 [1.7%]), pleomorphic cell sarcoma (2 [1.7%]), primary mediastinal (thymic) large B-cell lymphoma (2 [1.7%]), spindle cell sarcoma (2 [1.7%]), Ewing sarcoma (1 [0.8%]), follicular dendritic cell sarcoma (1 [0.8%]), gliosarcoma (1 [0.8%]), mucosa-associated lymphoid tissue lymphoma (1 [0.8%]), mantle cell lymphoma (1 [0.8%]), natural killer cell leukemia (1 [0.8%]), prolymphocytic T-cell leukemia (1 [0.8%]), rhabdomyosarcoma (1 [0.8%]), and therapy-related myeloid neoplasm, not otherwise specified (1 [0.8%]).

Table 2. Multivariate Logistic Regression Model

Factor	Odds ratio (95% CI)	*P* value
Age at first immune checkpoint inhibitor cycle		
≥70 y vs <70 y	2.32 (1.19-4.59)	.01
Sex		
Male vs female	1.75 (0.87-3.78)	.12
Cancer type (organ)		
Melanoma vs nonskin cancer	3.21 (1.51-6.58)	<.001
Nonmelanoma skin cancer vs nonskin cancer	8.32 (2.81-21.13)	

From the Firth univariate logistic regression model, age 70 years or older (OR, 2.38; 95% CI, 1.23-4.70; $P = .01$) and male sex (OR, 1.98; 95% CI, 0.99-4.27; $P = .05$) and having either melanoma or nonmelanoma skin cancer (NMSC) (melanoma: OR, 3.23; 95% CI, 1.53-6.60; $P < .01$ and NMSC: OR, 9.94; 95% CI, 3.38-24.98; $P < .01$) were associated with increased risk for ICI-induced BP. In the multivariate logistic regression model, age 70 years or older (OR, 2.32; 95% CI, 1.19-4.59; $P = .01$) and having skin cancer (melanoma: OR, 3.21; 95% CI, 1.51-6.58; $P < .01$ and NMSC: OR, 8.32; 95% CI, 2.81-21.13; $P < .01$) were significantly associated with increased risk for ICI-induced BP (**Table 2**).

Table 3. Propensity Score–Matched Univariate Logistic Regression, 1:2 Case-Control Matching

Characteristic	Overall, No. (%) (n = 105)	BP status, No. (%)		Odds ratio (95% CI)	*P* value
		No BP (n = 70)	BP (n = 35)		
Sex					
Male	67 (63.8)	42 (60.0)	25 (71.4)	1 [Reference]	.25
Female	38 (36.2)	28 (40.0)	10 (28.6)	0.60 (0.24-1.41)	
Race and ethnicity					
White	101 (96.2)	68 (97.1)	33 (94.3)	1 [Reference]	.48
Other[a]	4 (3.8)	2 (2.9)	2 (5.7)	2.06 (0.24-17.80)	
Cancer stage					
Non-stage IV	25 (23.8)	19 (27.1)	6 (17.1)	1 [Reference]	.26
Stage IV	80 (76.2)	51 (72.9)	29 (82.9)	1.80 (0.67-5.40)	
Cancer status at time of first ICI cycle					
No distant metastases	23 (21.9)	15 (21.4)	8 (22.9)	1 [Reference]	.87
Distant metastases	82 (78.1)	55 (78.6)	27 (77.1)	0.92 (0.35-2.53)	
Site of distant metastases					
Brain					
No	91 (86.7)	59 (84.3)	32 (91.4)	1 [Reference]	.29
Yes	14 (13.3)	11 (15.7)	3 (8.6)	0.50 (0.11-1.75)	
Skin					
No	95 (90.5)	64 (91.4)	31 (88.6)	1 [Reference]	.64
Yes	10 (9.5)	6 (8.6)	4 (11.4)	1.38 (0.33-5.17)	
Medical history					
Type 2 diabetes					
No	80 (76.2)	53 (75.7)	27 (77.1)	1 [Reference]	.87
Yes	25 (23.8)	17 (24.3)	8 (22.9)	0.92 (0.34-2.36)	
Cerebrovascular disease					
No	92 (87.6)	61 (87.1)	31 (88.6)	1 [Reference]	.83
Yes	13 (12.4)	9 (12.9)	4 (11.4)	0.87 (0.22-2.92)	
Neurocognitive disease					
No	102 (97.1)	68 (97.1)	34 (97.1)	1 [Reference]	.99
Yes	3 (2.9)	2 (2.9)	1 (2.9)	1 (0.05-10.80)	
Autoimmune disease					
No	95 (90.5)	63 (90.0)	32 (91.4)	1 [Reference]	.81
Yes[b,c]	10 (9.5)	7 (10.0)	3 (8.6)	0.84 (0.17-3.26)	
Vaccination within 6 mo before ICI					
No	87 (82.9)	58 (82.9)	29 (82.9)	1 [Reference]	.99
Yes	18 (17.1)	12 (17.1)	6 (17.1)	1 (0.32-2.86)	
Radiation before ICI					
No	68 (64.8)	47 (67.1)	21 (60.0)	1 [Reference]	.47
Yes	37 (35.2)	23 (32.9)	14 (40.0)	1.36 (0.58-3.15)	
Initial tumor response to ICI					
Stable disease or progression of disease	39 (37.1)	32 (45.7)	7 (20.0)	1 [Reference]	.01
Complete or partial response	66 (62.9)	38 (54.3)	28 (80.0)	3.37 (1.35-9.30)	
BMI >25					
≤25	40 (38.1)	27 (38.6)	13 (37.1)	1 [Reference]	.89
>25	65 (61.9)	43 (61.4)	22 (62.9)	1.06 (0.46-2.49)	
BMI >30					
≤30	82 (78.1)	55 (78.6)	27 (77.1)	1 [Reference]	.87
>30	23 (21.9)	15 (21.4)	8 (22.9)	1.09 (0.40-2.83)	
dNLR[d]					
≤3.0	78 (74.3)	55 (78.6)	23 (65.7)	1 [Reference]	.16
>3.0	27 (25.7)	15 (21.4)	12 (34.3)	1.91 (0.77-4.73)	

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, bullous pemphigoid; dNLR, derived neutrophil-to-lymphocyte ratio; ICI, immune checkpoint inhibitor.

[a] In the no BP group (70), other race and ethnicity included Asian and Pacific Islander (1 [1.4%]) individuals and those with unspecified race and ethnicity (1 [1.4%]). In the BP group (35), other race and ethnicity included Asian and Pacific Islander individuals (1 [2.9%]) and Hispanic or Latino individuals (1 [2.9%]).

[b] Autoimmune diseases among the patients who developed BP (35) included Hashimoto disease (3 [8.6%]).

[c] Autoimmune diseases among the patients in the no BP group (70) included Crohn disease (2 [2.9%]), immune thrombocytopenic purpura (1 [1.4%]), multiple sclerosis (1 [1.4%]), psoriasis (1 [1.4%]), psoriatic arthritis (1 [1.4%]), and rheumatoid arthritis (1 [1.4%]).

[d] The dNLR was calculated as dNLR = (absolute neutrophil count)/(white blood cell count − absolute neutrophil count). For each patient, blood cell counts used in the dNLR formula were taken from the same complete blood count on the day of receiving the first ICI cycle.

In the nested 1:2 case-control analysis, the 35 ICI-induced BP cases were compared with 70 propensity score-matched controls (**Table 3**). An initial complete or partial response on restaging imaging compared with stable disease or progression of disease was a risk factor for the development of ICI-induced BP (OR, 3.37; 95% CI, 1.35-9.30; $P = .01$). No other variables were risk factors for ICI-induced BP development. Patients with ICI-induced BP were more likely to have best overall complete or partial tumor responses to ICIs compared with all controls (29 of 35 [82.9%] vs 43 of 70 [61.4%]; $P = .03$) and controls without dermatologic adverse events (29 of 35 [82.9%] vs 18 of 37 [48.6%]; $P = .003$) (eTable in the Supplement).

Discussion

In this study, we investigated all ICI-induced BP cases across our institutions in a large retrospective cohort and nested case-control analysis to identify risk factors for BP among patients treated with ICIs. We found that 0.6% of individuals treated with ICIs developed BP and that age 70 years or older, being treated for melanoma or NMSC, and initial tumor response assessed on restaging imaging were associated with an elevated risk for ICI-induced BP. In the general population, the mechanistic association between age and BP remains unclear; however, our findings in individuals treated with ICI parallels the increased risk for idiopathic BP in patients aged 70 years or older, suggesting that ICIs may exacerbate an underlying propensity for BP development in older individuals.[5]

Immune checkpoint inhibitor–induced BP has been previously reported in patients with melanoma and cutaneous squamous cell carcinoma who were treated with anti-PD-1 therapy.[4,11] A population-level association between melanoma and BP has been recently reported; although the mechanism is unclear, contributing factors may include observed increased anti-BP antigen 2 (also known as BP180) autoantibodies among patients with melanoma and human leukocyte antigen variants associated with both melanoma and BP (*HLA-DQB1*03:01*).[12] Immune checkpoint inhibitor–induced immune activation may exacerbate this underlying preexisting risk. The roughly 2-fold discrepancy between the ORs for melanoma and NMSC may reflect differences in tumor biology that have yet to be ascertained, but these differences should be investigated in future translational work. Interestingly, tumor response to ICI—typically assessed after 3 to 4 cycles—is associated with the development of ICI-induced BP at any point (months or years) later in the patient's treatment course. Using initial tumor response assessed on imaging as a proxy for antitumor response, these results corroborate existing associations between broader dermatologic adverse event induction and improved overall survival and progression-free survival.[13]

We recommend that patients aged 70 years and older and those being treated for melanoma or NMSC be counseled about the risk for BP before ICI initiation. In addition, given the association of ICI-induced BP with improved initial and overall tumor response, early identification of this toxic effect is important; in patients who initially respond to ICIs and develop pruritic, eczematous, urticarial, erosive, or vesiculobullous eruptions, ICI-induced BP should be considered. Checkpoint inhibition should be preserved with appropriate toxic effect–directed treatment whenever possible. Optimal management beyond topical steroids warrants further study; reported treatments include systemic corticosteroids and biologic (ie, rituximab, omalizumab, dupilumab) and nonbiologic options (tetracycline antibiotics, methotrexate, mycophenolate mofetil) for refractory cases.[2,14,15] The implications of these interventions for the ICI-mediated antitumor effect is an area of active study.

Limitations

This study has limitations, including the retrospective data collection, small case number given the rarity of ICI-induced BP, and lack of known causal mechanisms underlying all identified risk factors for ICI-induced BP. The case number necessitated collapsing cancer type into 3 groups (nonskin, melanoma, and NMSC) to maximize subgroup size for statistical comparison in the multivariate logistic regression model. In addition, patients who received ICIs within double-blinded clinical trials were unavailable for propensity score matching, which may have affected control selection, particularly for cancer types in which ICIs have yet to be fully approved.

Conclusions

This research suggests that patients who receive ICIs after age 70 years or for treatment of skin cancer have an increased risk for developing BP, and patients who develop ICI-induced BP have relatively improved tumor responses. Future work identifying risk factors and implications for other dermatologic adverse event phenotypes would be important for dermatologists, oncologists, and patients alike.

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