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Cutaneous adverse events of immune checkpoint inhibitor therapy: incidence and types of reactive dermatoses *

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Abstract

Background: Dermatoses are common and potentially serious complications of programmed cell death receptor PD-1 immune checkpoint inhibitor (anti-PD-1 ICI) therapy. Understanding their incidence is necessary to support clinical awareness, diagnosis, and management.

Objective: To examine the incidence and odds of reported non-cancerous dermatoses in the setting of anti-PD-1 ICI therapy.

Methods: Cross-sectional study of anti-PD-1 (pembrolizumab or nivolumab) treated patients at a tertiary healthcare institution. Selected dermatologic events following immunotherapy were identified in the electronic medical record. Comparator arm were patients that developed these same dermatoses without receiving anti-PD-1 ICI therapy.

Results: There were 13.7% (254/1857) patients that developed one of 28 dermatoses. Compared with the general population, patients treated with anti-PD-1 had a greater risk for development of mucositis (OR 65.7, 95% CI 35.0–123.3), xerostomia (OR 11.9, 95% CI 8.4–16.8), pruritus (11.3, 95% CI 8.9–14.3), and lichen planus/lichenoid dermatitis (OR 10.7, 95% CI 5.6–20.7).

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Disclosure statement

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Ethical approval

IRB approval was waived, as only anonymous aggregate-level data counts were used.

Conclusions: We report the frequency of dermatoses encountered in the setting of ICI therapy, both common (pruritus, rash, vitiligo) and uncommon (scleroderma, urticaria).

Keywords

Nivolumab; pembrolizumab; irAE; drug reaction

Introduction

The development of programmed cell death receptor PD-1 immune checkpoint inhibitors (anti-PD-1 ICIs) represents a major advancement in cancer immunotherapy. This new class of monoclonal antibodies works by inhibiting immune checkpoint signals, which prevent T-cell activation and allow tumor cells to evade recognition by the immune system. These agents thus facilitate the reactivation of an adaptive immune response and the establishment of anti-tumor activity. Because of this novel mechanism of action, ICIs have a unique safety profile that include a distinct range of skin reactions (1,2).

Although these agents are better tolerated and associated with fewer systemic symptoms than traditional chemotherapy, they are associated with higher rates of adverse events compared to traditional chemotherapy (3). Cutaneous adverse events seen in the setting of ICI therapy have been reported in up to one-third of treated patients, and are usually the first adverse event to occur with immune checkpoint inhibitor use, including anti-PD-1 therapy (1). The majority of these cutaneous events include pruritus, vitiligo, and rash (4).

With the increasing development and use of immunotherapy agents in oncology, comprehensive cancer care necessitates an improved understanding of the various dermatologic conditions associated with this class of agents in real-world clinical environments. We aimed to describe the incidence of a known spectrum of skin dermatoses in the setting of anti-PD-1 therapy, and also identify the relative risk of these adverse events compared with the general population.

Materials and methods

This is a cross-sectional single-institution study examining the presence of reported dermatoses in the setting of ICI therapy at Johns Hopkins Healthcare Systems (JHHS). This study did not require IRB approval, due to the use of anonymized and de-identified aggregate-level data. Data was compiled using EPIC.

A list of inflammatory dermatoses occurring in the setting of anti-PD-1 therapy (pembrolizumab or nivolumab) was compiled using our institutional experience with ICIs and involved a literature search of case studies and reports on PUBMED. The list of identified dermatoses in the reported literature is shown in Table 1. Patients aged 18+ were identified from September 15th, 2014, to November 1st, 2018 that were documented to have received at least one dose of pembrolizumab or nivolumab as monotherapy at JHHS. Additional filters were applied to document the number of patients with a known cutaneous event within a 2-year span after receiving anti-PD-1 therapy. Patients were excluded if they had a prior diagnosis of the cutaneous event. The 2-year span was chosen after a review

of clinical case studies due to significant heterogeneity in time to the presentation of these events following ICI therapy in the literature (32). SNOMED-CT concepts were used to search for cutaneous adverse events within this population, with alternate SNOMED-CT concepts used for common disease classifications noted in Table 1. A control group was identified of patients aged 18+ presenting to JHHS who have never received pembrolizumab or nivolumab.

Baseline demographic factors (Table 2) were characterized by the percentage of the total for categorical variables. After excluding all events with less than 5 observations, unadjusted odds ratios (OR) for the development of a given cutaneous event between the study and control populations were calculated and are presented in Table 3. A Bonferroni correction was applied to account for multiple comparisons, with the alpha level being set at 0.005 (alpha = (0.05)/(11 independent comparisons)). ORs were not calculated for cutaneous adverse events with less than 5 observations after administration of pembrolizumab or nivolumab.

Results

The demographic characteristics of the two study arms are reported in Table 2. There were 4,856,827 patients over 18 years of age seen at JHHS between September 15, 2014 and November 1, 2018, and 1857 patients treated with anti-PD-1 ICI, either pembrolizumab or nivolumab. Of the patients treated with anti-PD-1 ICIs, 58.2% were male, and 41.8% were female. White/Caucasian was the most common race (81.3%), and 85.7% of patients were between the ages of 50-89. In the comparator arm, the 4,854,970 patients were never treated with anti-PD-1 therapy, 45.5% were male and 54.2% were female. White/Caucasian was also the most common race (54.1%) and 49.5% of patients were between the ages of 50–89 years.

Of the 1857 patients treated with anti-PD-1 ICIs, there were 1079 patients treated with nivolumab, 821 patients treated with pembrolizumab, and 43 patients treated with both pembrolizumab and nivolumab. There were 254/1857 (13.7%) patients who developed one of the 28 different dermatoses identified from the literature review following anti-PD-1 ICIs. Eleven reactions, although reported in the literature, had an incidence $n < 5$: xerosis ($n = 4$), Stevens-Johnson syndrome ($n = 2$), paronychia ($n = 2$), panniculitis ($n = 2$), onycholysis ($n = 2$), maculopapular eruption ($n = 2$), bullous pemphigoid ($n = 2$), alopecia areata ($n = 2$), acral erythema ($n = 2$), Grover's disease ($n = 2$), and erythema multiforme ($n = 2$), as reported in Table S1. 6 reactions had an incidence of $n = 0$. This included dermatomyositis, erythroderma/pityriasis rubra pilaris, granuloma annulare, hyperkeratosis, photosensitivity, and subacute cutaneous lupus erythematosus (Table S1).

There were 11 reactions that occurred within 2 years and with $n \geq 5$; Table 3 shows those dermatoses with calculated odds ratios. In our study population, 13.0% (242/1857) developed one of the final 11 cutaneous events included in our analysis. The cutaneous adverse events with highest incidence were pruritus ($n = 71$, 3.8%), eczema or atopic dermatitis ($n = 65$, 3.5%), xerostomia ($n = 33$, 1.8%), psoriasis ($n = 17$, 0.9%), hyperhidrosis ($n = 11$, 0.6%), and mucositis ($n = 10$, 0.5%). Compared with the population of patients not

treated with ICIs during this time period, patients treated with anti-PD-1 had significantly greater odds of developing 9 dermatoses including mucositis (OR 65.7, 95% CI 35.0–123.3), xerostomia (OR 11.9, 95% CI 8.4–16.8), pruritus (OR 11.3 95% CI 8.9–14.3), lichen planus or lichenoid dermatitis (OR 10.7, 95% CI 5.6–20.7), scleroderma (OR 9.3, 95% CI 4.2–20.9), vitiligo (OR 7.7, 95% CI 3.4–17.2), eczema or atopic dermatitis (OR 3.3, 95% CI 2.6–4.3), psoriasis (OR 3.2, 95% CI 2.0–5.2), and hyperhidrosis (OR 2.8, 95% CI 1.6–5.1). Urticaria ($p = .5$) and rosacea ($p = .3$) were not significantly different between the study and control populations.

Discussion

This data shows that 14% of the study population developed one of the 28 cutaneous events originally identified in our literature review, and 13% developed one of the final 11 cutaneous events included in our analysis. The highest incidence dermatoses in the setting of anti-PD-1 ICIs included pruritus, eczema or atopic dermatitis, and xerostomia. When compared to the general population, patients on anti-PD1 ICI therapy were significantly more likely to present with mucositis, xerostomia, pruritus, and lichenoid dermatitis or lichen planus. Although there exists single institutional data on cutaneous events associated with anti-PD-1 therapy (9,30,33,34), this report is the first study to report risk for cutaneous events in the setting of anti-PD-1 therapy as compared to the general population.

While cutaneous events in the setting of ICI therapy pose a significant adverse event over the course of treatment, it has been suggested that the appearance of cutaneous events in the setting of ICI may indicate a greater likelihood for achieving an anti-tumor response (30). This has been shown in melanoma (35,36), non-small-cell lung cancer (37,38), renal cell carcinoma (39), and other tumor types (40). Associations with tumor response and survival of any of the aforementioned dermatoses were not in the scope of this study and will be an area for further investigation.

Because of the nonspecific diagnosis of ‘rash’ that has been frequently reported in many anti-PD-1 clinical trials, the incidence of clinical phenotypes of rash, for example, eczema, lichenoid dermatitis, oral mucositis, or urticaria, remains poorly understood (7). This documentation may be limited by the awareness and skill of the person documenting in the electronic medical record. Disaggregation and more precise terms, as performed in this study, could thus provide valuable insight into the incidence of specific dermatoses. One example of the usefulness of disaggregation is with urticaria. Although urticaria has been seen with a pooled incidence rate of 1.4% (6/427) with the administration of nivolumab (14), in our analysis we did not observe a significant association between urticarial dermatoses and anti-PD-1 therapy. Discrepancies like this could be explained by providers not having the dermatologic knowledge to code these events in detail, further highlighting the necessity for dermatology input within multi-disciplinary teams caring for these complex patients. In contrast, lichen planus or lichenoid dermatitis is 10.7-fold more likely to develop in those treated with nivolumab or pembrolizumab than the general population (95% CI 5.6–20.7), which is consistent with prior findings (34).

The incidence and ORs reported for dermatoses in this study may not be representative of the true incidence and ORs due to several factors. Although the most common dermatoses seen in the setting of anti-PD-1 therapy are reported to be rash, pruritus, and vitiligo (1,14,41), we found that pruritus (at an incidence of 3.8%) was the only one of these dermatoses to be highly represented in our cohort. In general, the incidence rates found in our study are globally lower compared to those reported in the literature, or not seen at all. For example, all-grade pruritus was found in a meta-analysis analysis of PD-1 clinical trials to have an incidence of 20.2% (35/184) for pembrolizumab and 13.2% (164/1126) for nivolumab (14). Compared to our incidence of 3.8% for pruritus, discrepancies like this could be explained by the relatively heightened surveillance when conducting clinical trials.

Limitations of our study include the absence of de-aggregated individual patient-level data, which limits our ability to make granular conclusions based on tumor type or staging within our sampled patient population. Rare dermatoses in the setting of anti-PD-1 therapies identified in the literature, such as photosensitivity and subacute cutaneous lupus erythema, were not seen in our patient population. These dermatoses might have appeared with larger sample size or more accurate reports upon reviewing patient charts and pathology reports. In addition, the single-institution nature of the analysis limits the generalizability of the results. Due to limitations in data collection, we did not explore the severity, treatment, and outcome of these various dermatoses. This will be a topic for further exploration. Finally, although we established temporality by identifying the appearance of these dermatoses after the administration of pembrolizumab or nivolumab, we are unable to definitively establish causality or relationship to particular tumor types. Despite these limitations, the associations reported in this study between cutaneous adverse events and these anti-PD-1 therapies motivate future investigation. As nivolumab and pembrolizumab currently make the bulk of approvals for ICI therapy, a better understanding of the epidemiology, risk factors, and clinical outcomes of these cutaneous events in a real-world clinical setting is necessary to provide a tailored risk assessment for patients commencing these therapies. Further studies are needed to assess dose-response relationships, prognostic information from cutaneous events, and outcomes to treatment for these cutaneous events.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Identified list of dermatoses arising in the setting of anti-PD-1 ICI therapy.

Dermatoses	Citation
Acral erythema	(5)
Alopecia areata	(6)
Bullous pemphigoid	(7)
Dermatomyositis	(8)
Eczema or atopic dermatitis	(9)
Erythema multiforme	(10)
Erythroderma or pityriasis rubra pilaris	(11)
Granuloma annulare	(12)
Grover's disease[a]	(13)
Hyperhidrosis	(14,15)
Hyperkeratosis	(16)
Lichen planus or lichenoid dermatitis	(9)
Maculopapular eruption	(1)
Mucositis[b]	(13)
Onycholysis	(1)
Panniculitis	(17,18)
Paronychia	(19)
Photosensitivity	(20)
Pruritus[c]	(21)
Psoriasis	(22,23)
Rosacea	(24)
Scleroderma[d]	(25,26)
Stevens-Johnson syndrome	(27)
Subacute cutaneous lupus erythematous	(8,28)
Urticaria	(29)
Vitiligo	(9)
Xerosis[e]	(30)
Xerostomia	(31)

[a] Searched for with SNO-MED code 'transient acantholytic dermatosis.'

[b] Searched for with SNO-MED code 'mucositis following therapy.'

[c] Searched for with SNO-MED code 'itching.'

[d] Searched for with SNO-MED code 'sclerosis of the skin.'

[e] Searched for with SNO-MED code 'dry skin.'

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Table 2.

Demographics of general population at JHHS and population receiving anti-PD-1 treatment.

Characteristic	Never treated with anti-PD-1 therapy % (*n* = 4,854,970)	Anti-PD-1 therapy treatment % (*n* = 1857)	*p*-Value[a]
Sex			
Male	45.5	58.2	<.001
Female	54.2	41.8	<.001
Unknown/other	0.3	0	.18
Race			
White/Caucasian	54.1	81.3	<.001
Black/African American	19.1	12.0	<.001
Asian	3.3	3.2	.81
American Indian or Alaskan native	0.2	0.3	.33
Native Hawaiian/Other Pacific Islander	0.05	0.2	.0039
Other	5.8	2.3	<.001
Unknown	17.3	0.2	<.001
Declined to answer	0.2	0.1	.33
Age			
18–29	13.5	1.9	<.001
30–39	14.5	3.3	<.001
40–49	14.1	7.3	<.001
50–59	16.4	19.9	<.001
60–69	15.1	29.6	<.001
70–79	11.2	25.6	<.001
80–89	6.8	10.6	<.001
90+	8.4	1.7	<.001

[a]Chi-squared test comparing two populations for given characteristic.

Table 3.

Incidence, OR, 95% CI, and *p*-values for cutaneous adverse events in both the general population and after receiving anti-PD-1 treatment with $n > 5$ cases.

Cutaneous adverse event	General population, *n* (%)[a]	PD-1, *n* (%)[b]	OR (95% CI)	*p*-Value[c]
Pruritus	17,132 (0.4)	71 (3.8)	11.3 (8.9, 14.3)	<.005
Eczema or atopic dermatitis	52,243 (1.1)	65 (3.5)	3.3 (2.6, 4.3)	<.005
Xerostomia	7396 (0.2)	33 (1.8)	11.9 (8.4, 16.8)	<.005
Psoriasis	13,942 (0.3)	17 (0.9)	3.2 (2.0, 5.2)	<.005
Hyperhidrosis	10,231 (0.2)	11 (0.6)	2.8 (1.6, 5.1)	<.005
Mucositis	425 (0.009)	10 (0.5)	65.7 (35.0, 123.3)	<.005
Lichen planus or lichenoid dermatitis	2217 (0.05)	9 (0.5)	10.7 (5.6, 20.7)	<.005
Rosacea	10,607 (0.2)	6 (0.3)	1.5 (0.7, 3.3)	0.3
Scleroderma	1689 (0.03)	6 (0.3)	9.3 (4.2, 20.9)	<.005
Urticaria	11,989 (0.2)	6 (0.3)	1.3 (0.6, 2.9)	0.5
Vitiligo	2052 (0.04)	6 (0.3)	7.7 (3.4, 17.2)	<.005

[a] Denominator is the 4,856,827 patients seen at JHHS from September 15, 2014 to November 1, 2018.

[b] Denominator is the 1857 patients treated with anti-PD-1 therapy at JHHS from September 15, 2014 to November 1, 2018.

[c] Corrected for multiple comparisons, with alpha level set at 0.005.