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LETTER TO THE EDITOR

Spectrum of PD-1 and PD-L1 inhibitor cutaneous adverse events in skin of color: a retrospective, single-institutional study in an urban community

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Introduction

Programmed cell death 1 (PD-1) and programmed death-ligand 1 (PD-L1) have emerged as popular targets for immune checkpoint inhibitors given the numerous malignancies that have been found to upregulate these proteins to induce T-cell exhaustion and evade immune destruction [1]. Owing to their efficacy as antitumor treatments, PD-1 and PD-L1 inhibitors are becoming standard of care for various metastatic and locally aggressive malignancies including non-small-cell lung cancer and melanoma [2]. Despite their success as antitumor treatments, use of PD-1 and PD-L1 inhibitors is limited by their broad spectrum of toxicities ranging from mild to potentially fatal [3]. Injury to multiple organ systems has been documented in the literature with cutaneous adverse events being one of the most common [3,4]. Cutaneous adverse events associated with PD-1/PD-L1 inhibitors are being increasingly characterized for their wide spectrum of presentation but have not been evaluated in an urban setting with primarily people of color (POC). Access to dermatologic care in more ethnically diverse communities may be skewed as studies have shown that there are fewer dermatologists in urban zip codes with more POC [5]. Insufficient educational resources regarding skin of color may contribute to variations in patient presentation and diagnosis between POC and white patients [6]. To the best of our knowledge, this is the first study to explore the spectrum of cutaneous adverse events in patients with skin of color compared to ethnically white patients.

Methods

We conducted a retrospective analysis of the electronic medical records of a tertiary academic medical center with a dedicated supportive oncodermatology service and identified patients who received PD-1 or PD-L1 immunotherapy from 2016 to 2019 and referred to dermatology. Patients from that cohort were then evaluated for possible cutaneous adverse events from their immunotherapy. Dermatological findings were separated into 15 categories for comparison. Cases with unusual morphologies that cannot be described with classic nomenclature were listed as 'other.' Method of diagnosis, treatment, and outcomes of cutaneous adverse events were recorded. Causality was assessed with WHO-UMC causality categories: certain, probable/likely, possible, unlikely, conditional/unclassified, and unassessable/unclassifiable. Grading of adverse events was assigned per the National Cancer Institute Cancer Therapy Evaluation Program (CTEP) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, ranging from 1 to 5. Patient demographics, including gender, race, and ethnicity were summarized.

Results

Electronic medical records identified 642 patients receiving PD-1/PD-L1 inhibitor therapy. PD-1/PD-L1 treatments in our patient population included the PD-1 inhibitors nivolumab and pembrolizumab and the PD-L1 inhibitors atezolizumab, durvalumab, and avelumab. Of the 642 patients, 45 patients were determined to have possible cutaneous adverse events associated with treatment and six patients determined to have two dermatological diagnoses. These patients were being treated for a wide variety of different cancers including lung (25, 56%), melanoma (7, 16%), liver (5, 11%), renal (2, 5%), hypopharyngeal (1, 2%), gallbladder (1, 2%), Hodgkin lymphoma (1, 2%), ovarian (1, 2%), thymic (1, 2%), and Merkel (1, 2%). Patients in our cohort were classified as white non-Spanish/Hispanic/Latino (124, 19.3%), POC (439, 68.4%), or unknown (79, 12.3%). The POC group consisted of American Indian or Alaskan Native, Asian, black or African American, and 'other' Spanish/Hispanic/Latino patients. The unknown group included patients who declined to or were unable to provide demographic data and patients listed as 'other' by race but declined or were unable to report an ethnicity. Our sample comprised of 16 black (36%), 15 white (33%), nine other (Hispanic or Latino) (20%), four Asian (9%), and one Native American (2%) patients, of which, 25 were male and 20 were female (Table 1). Patients in the 'other' race category were all ethnically Hispanic or Latino.

Cutaneous adverse events were graded per CTEP guidelines with the average as 1.7 ± 0.5 among the 15 white patients and 1.5 ± 0.8 among the 30 POC patients with no significant difference observed between the two groups

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Table 1. Demographics, study data, and breakdown of cutaneous adverse events in ethnically white and POC patients treated with PD-1/PD-L1 inhibitors.

	White, non-Hispanic	Person of color	Total
1.1. Demographics			
Count (# of people)	15	16 Black 9 Other (Hispanic/Latino) 4 Asian 1 Native American 30 Total	45
Age (years)	70.7 ± 8.0	67.9 ± 9.2	69.3 ± 9.1
Male:female	2:1	1:1	1.25:1
Malignancy (# of types)	6 Lung 3 Melanoma 1 Liver 1 Renal 1 Hypopharyngeal 1 Hodgkin 1 Thymic 1 Merkel	19 Lung 4 Melanoma 4 Liver 1 Renal 1 Gallbladder 1 Ovarian	25 Lung 7 Melanoma 5 Liver 2 Renal 1 Hypopharyngeal 1 Gallbladder 1 Hodgkin 1 Ovarian 1 Thymic 1 Merkel
1.2. Study data			
Grade	1.7 ± 0.5	1.5 ± 0.8	1.6 ± 0.7
Biopsy required	4	12	16
Stopped treatment	2	11	13
Flare-up of underlying condition	1	2	3
1.3. Cutaneous adverse events			
Bullous	0	2	2 (0.04)
Eczematous dermatitis	2	8	10 (0.20)
Hyperpigmentation	0	1	1 (0.02)
Lichenoid	1	6	7 (0.14)
LSEA	0	1	1 (0.02)
Morbilliform	4	1	5 (0.10)
Other	1	2	3 (0.06)
Pruritus	1	3	4 (0.08)
Psoriasis	3	2	5 (0.10)
Sarcoidosis	0	1	1 (0.02)
Sweet's syndrome	0	1	1 (0.02)
Vitiligo	0	3	3 (0.06)
Xerosis	0	3	3 (0.06)
Undefined	4	0	4 (0.08)
VV + KA	1	0	1 (0.02)
Total	17	34	51 (1)

LSEA: lichen sclerosus et atrophicus; VV + KA: verruca vulgaris with features of keratoacanthoma.
(1.1) Demographics of patients with cutaneous adverse events from PD-1/PD-L1 immunotherapy. (1.2) Study data included grade, skin biopsy performed, treatment cessation, and flare-up of underlying dermatologic condition. (1.3) Spectrum of cutaneous adverse event presentations in white and POC patients. Six patients were determined to have two dermatological diagnoses. Parenthetical numbers indicate percentage of all cutaneous adverse events.

($p = .31$). On average, 27% of white patients required skin biopsies while 40% of POC patients required biopsies ($p = .39$). Thirteen patients stopped treatment due to unacceptable side effects or to pursue alternative therapies or palliative care. Two patients with underlying psoriasis and one with underlying lichen sclerosus flared with PD-1/PD-L1 treatment. (Table 1) (Figure 1(A)).

Both ethnically white and POC patients exhibited a wide spectrum of presentations with eczematous dermatitis (10, 20%) being the most common cutaneous adverse event overall. Within our patient population, eczematous and lichenoid presentations were more prevalent in POC patients than in white patients ($p = .32$ and $p = .25$, respectively) (Table 1).

The cutaneous adverse events exhibited are consistent with those identified in the literature [4,7]. In addition to expected findings such as vitiligo (3, 6%) and morbilliform eruptions (5, 10%), numerous patients presented with new onset lichenoid dermatitis (7, 14%) and few patients presented with bullous disease (2, 4%) (Figure 1(B-D)). Overall, there were no differences in distribution of cutaneous adverse events between white and POC patients.

Discussion

The wide spectrum of cutaneous adverse events associated with PD-1 and PD-L1 inhibitors is well characterized in the literature; however, no studies have examined and compared the distribution of cutaneous adverse events in ethnically white and POC patients [3,7]. To attempt to limit this knowledge gap, we conducted a retrospective, single-institutional study to characterize the cutaneous adverse events in our diverse urban community and determine if there were any tangible differences in cutaneous adverse events between ethnically white and POC patients.

Of the 45 patients with cutaneous adverse events associated with PD-1/PD-L1 inhibitor therapy, 15 were ethnically white and 30 were POC (black, 'other' Hispanic/Latino, Asian, Native American). Though the number of POC patients with cutaneous adverse events were double that of white patients, these numbers are in line with the demographics of our largely black and Hispanic community (our cohort was 19.3% ethnically white, 68.4% POC, and 12.3% unknown) [8]. Previous research has shown that there were

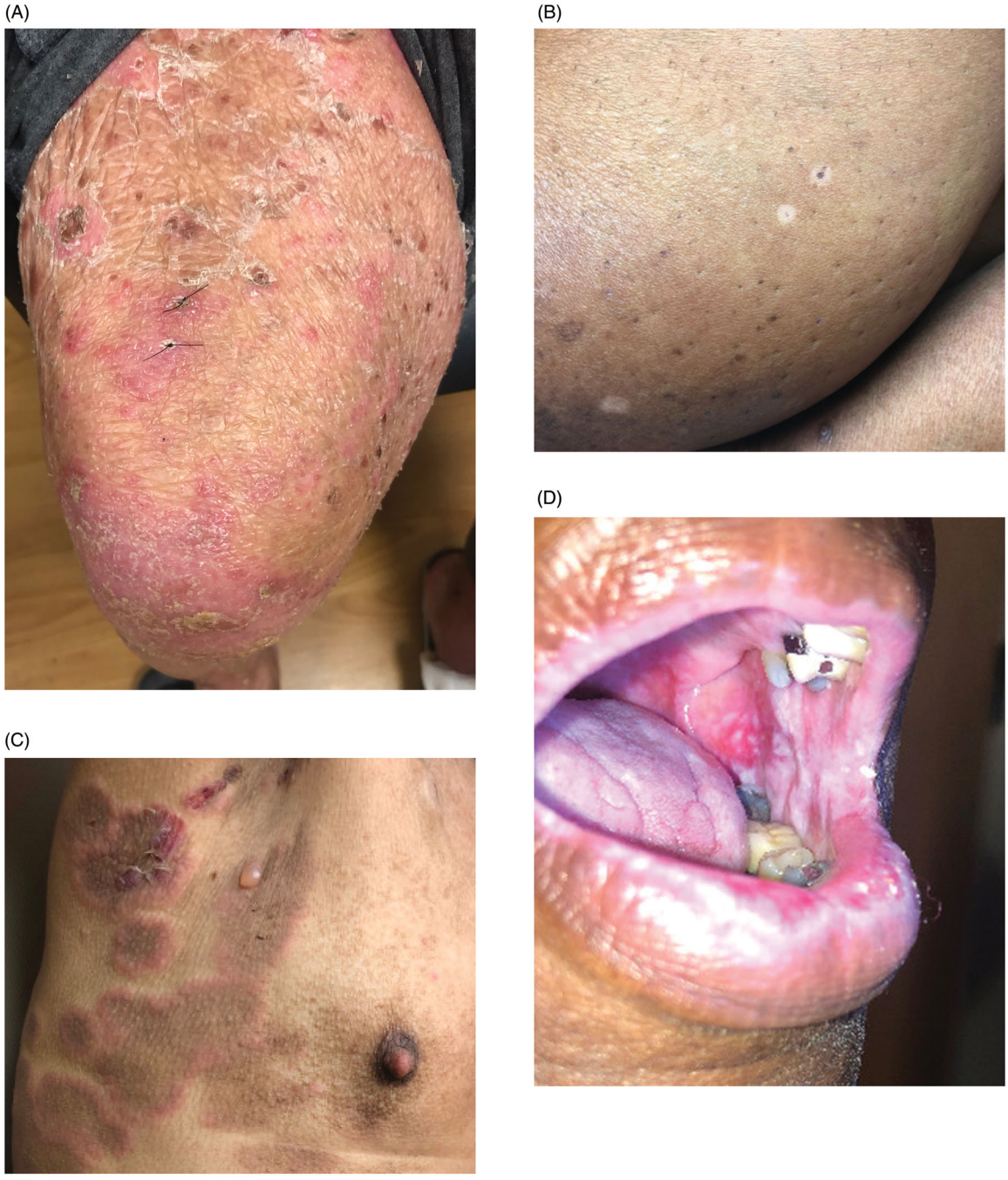

Figure 1. Cutaneous adverse events associated with PD-1/PD-L1 inhibitors as seen on skin of color. (A) Puerto Rican patient with exacerbation of underlying psoriasis and development of bullous pemphigoid in the setting of pembrolizumab. (B) Vitiligo in setting of nivolumab. (C) Autoimmune blistering disease in setting of pembrolizumab. (D) Mucosal lichenoid dermatitis in the setting of pembrolizumab.

no significant race-based disparities in the use of PD-1 inhibitors so that factor is unlikely to have contributed to the difference [9].

Thirteen people stopped treatment however most discontinuations were due to patient preference rather than life-threatening medication toxicities. In many cases, progression of disease and/or deconditioning prompted the patient and care team to pursue alternative therapies or palliative care. When therapy was discontinued due to drug intolerance (in eight patients), the following reasons were cited: headaches, dizziness, renal failure (unrelated to therapy), rash (lichenoid/eczematous dermatitis, bullous eruptions, and psoriasis flare), oral and salivary gland swelling, colitis, and arthritis. Many coexisting immune-related adverse events were noted within this population (adrenal insufficiency, anorexia, arthritis, colitis, confusion, cough, dysphagia, dyspnea, encephalopathy, esophagitis, fatigue, headache, hypothyroidism, mucositis, nausea, neuropathy, neutropenia, thrombocytopenia, and vomiting); however, these adverse events cannot be attributed solely to PD-1/PD-L1 use since many patients were on multi-drug regimens. Mild eosinophilia was a nonspecific finding seen in a few patients that may be attributed to allergic disease.

Our study population presented with a wide range of cutaneous adverse events with 51 dermatological diagnoses

between 45 patients; however, no novel cutaneous adverse events associated with PD-1/PD-L1 treatment were observed. Expected findings such as vitiligo, which can be seen in patients managed for melanoma, lichenoid reactions, pruritus, and morbilliform eruptions were typically low grade and did not warrant immediate cessation of therapy [7,10]. Within this population, eczema and lichenoid dermatitis may be slightly more common in POC patients than in white patients but given the small sample size it is difficult to determine statistical significance. Three patients flared with initiation of PD-1/PD-L1 therapy; however, most patients presented with new cutaneous eruptions. Patients with preexisting dermatological conditions starting on PD-1/PD-L1 therapy may have added benefit from having an established relationship with a dermatology provider since prompt management may prevent potential disease flares [11]. Cutaneous adverse events in certain cases may represent a positive response to treatment thus prompt recognition and management of these adverse events may help patients with skin of color to maintain their oncologic treatment successfully [10]. Due to differences in malignancies, treatment regimens, goals of treatment, and follow-up in this study population, a robust analysis cannot be performed to investigate whether the presence of immune phenomena were predictors of response to therapy.

Sixteen biopsies were collected due to unclear etiology, to rule out new/recurrent malignancy or cutaneous metastases, non-response to empiric therapy, and/or to determine if skin pathology was a drug eruption. There was only one instance where biopsy was taken due to concerning features (duskiness and associated pain). Interestingly, though no difference in grade or cutaneous adverse event distribution was appreciated between POC and white patients, 40% of skin of color patients required a skin biopsy compared to the 27% in white patients. Though the significance of this observation is limited by the small sample size, the higher percentage of biopsies in POC patients may reflect difficulties in diagnosing cutaneous adverse events on skin of color. Coverage of skin of color in dermatology educational resources is limited compared to coverage of fairer Fitzpatrick skin types so providers may have more trouble recognizing cutaneous adverse events on POC [6].

Limitations

Our study is limited by our small sample population which was obtained from a specialized oncodermatology center practicing in an urban environment. The only cases examined were of patients with cutaneous adverse events significant enough to merit referral to dermatology from oncology.

Conclusion

While larger studies looking at various communities may be helpful in identifying disparities in care, we seek to showcase and describe the presentations of various dermatologic processes in skin of color to aid in prompt diagnosis. Clinicians, particularly in oncology and dermatology, should be aware of the wide spectrum of cutaneous adverse events associated with PD-1/PD-L1 inhibitors as well as their presentations on different skin tones as they may look different in POC patients. Since urban dermatologists are disproportionally located in areas with smaller POC populations, being attune to different presentations of cutaneous adverse reactions is paramount [5]. The paucity of resources available to help researchers and clinicians recognize PD-1/PD-L1 cutaneous adverse effects on skin of color presents an area for continued research [6].

Ethical approval

The authors have no ethical conflicts to disclose. The Albert Einstein College of Medicine Institutional Review Board reviewed and approved this study (#2019-10622) and the patients have given informed consent to the writing of this article and publishing of pictures. This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

IRB approval status

Reviewed and approved by Einstein IRB; IRB #2019-10622.

Disclosure statement

The authors have no conflicts of interests to declare.

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