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Case and Review

Psoriasis Vulgaris Exacerbation during Treatment with a PD-1 Checkpoint Inhibitor: Case Report and Literature Review

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Psoriasis · Checkpoint inhibitors · Anti-PD-1 · Anti-PDL-1 · Immune-related adverse events

Abstract
Objective: The incidence of immune-related adverse events is growing as the use of checkpoint inhibitors is exponentially increasing. Cutaneous adverse events are among the most frequent immune-related adverse events. The purpose of this case report and literature review is to highlight psoriasis as a potential adverse event with need for early recognition. ***Case Report and Literature Review:*** We describe the case of a 65-year-old woman with psoriasis exacerbation while treated with nivolumab (anti-PD-1) for a stage IV melanoma. She had a history of scalp psoriasis but she presented with psoriatic lesions on both lower and upper limbs. Our patient was treated with topical steroids. So far, 34 other cases with an exacerbation of psoriasis during treatment with anti-PDL-1 or PD-1 therapy have been reported in the literature. A broad range of therapies are described, without any available guidelines for this particular condition. ***Conclusion:*** Psoriasis exacerbation is an established side effect of PD-1/PDL-1 checkpoint inhibitors with 35 reported cases. Early recognition and management are

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challenging as there are no clear guidelines available. A close collaboration between oncologist and dermatologist is mandatory to manage this immune-related adverse event.

Introduction

The use of immune checkpoint inhibitors (ICI) is exponentially increasing as it has become the standard of care for several cancer types. Currently, 2 types of ICI are used in the clinic: first, anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and second, anti-programmed cell death 1 (PD-1) or anti-programmed death ligand 1 (PD-L1) inhibitors. Inherent to the mechanism of action, immune-related adverse events (irAEs) are seen. Every organ is at risk, but skin toxicity is among the most frequent adverse events. Nonspecific maculopapular rash and pruritus represent the most common manifestations [1]. Other entities are less frequent and not so well documented. We present a case of psoriasis vulgaris exacerbation in a patient treated with nivolumab (anti-PD-1). The purpose of this paper is to point to the possibility of psoriasis vulgaris exacerbation as a potential irAE and to discuss the management of this adverse event.

Case Presentation

A 65-year-old woman presented with multiple itchy erythematosquamous plaques on both lower and upper limbs ongoing for 1 week. In addition, psoriasiform scales on the scalp and retroauricular were observed. Full-body inspection revealed no other skin lesions. The patient was in good general condition. She had no other complaints and felt generally well. She denied systemic complaints such as weight loss, night sweats, fever, dyspnea, cough, or gastrointestinal symptoms. The patient had been treated with nivolumab 3 mg/m^2 (anti-PD-1) every 2 weeks for a stage IV melanoma. At the time of presentation, the treatment had been administered 11 times. Two years ago, she was diagnosed with a stage IV melanoma, positive for the BRAF V600 mutation. She was diagnosed with lymph node, subcutaneous, and brain metastases. Nivolumab was initiated as a third-line treatment, after a BRAF enzyme inhibitor and ipilimumab (CTLA-4 inhibitor). Ipilimumab was stopped after 2 cycles because of grade 3 diarrhea. Since the treatment with nivolumab, a disease stabilization was observed. The patient had a known history of scalp psoriasis, type II diabetes, and hypertension. Her regular medication included lorametazepam, gliclazide, metoprolol, pantoprazole, and momethasone nasal spray.

Based on the clear clinical image, the patient was diagnosed with a psoriasis vulgaris exacerbation. The clinical image is shown in Figure 1. No skin biopsy was obtained. Local treatment with corticosteroids was initiated. Additionally, on patient request, the interval of nivolumab was extended from 2 weeks to 3 weeks, because she noticed a flare-up of the skin lesions after every nivolumab administration. Dosing at 3-week intervals, in combination with the local corticoid treatment, led to successful control of the psoriatic lesions. No systemic corticoids were administered. The patient had a stable disease for 14 months after the start of

nivolumab. Then, she developed progressive brain metastasis with an intracranial hemorrhage and died.

Literature Review

A bibliographic search was conducted on PubMed using the key words: "psoriasis" and "nivolumab," "pembrolizumab," "atezoluzimab," "anti PD-1," or "anti PDL-1." Thirty-four cases with psoriasis linked to anti-PD-1 or anti-PDL-1 treatment were retained. An overview is given in Table 1 and Table 2. Twelve individual cases were described. Two authors published a collection of 17 and 5 cases, respectively, in 1 publication [2, 3]. Two additional publications also reported on psoriasis exacerbation but were not included in the tables because detailed information is missing [4, 5].

Discussion

We describe an exacerbation of a mild pre-existing psoriasis under anti-PD-1 therapy. An extension of the disease with new localizations was observed. We hypothesize that nivolumab was the trigger to the psoriasis exacerbation in our patient. However, we should mention that a psoriasis exacerbation can be triggered by multiple factors, such as stress and skin injury. In our case, the sequence of events and a clearly observed flare-up of the lesions after each anti-PD-1 infusion suggest a causal link between the administration of nivolumab and the psoriasis exacerbation. Indeed, several cases of psoriasis exacerbation following PD-1 or PDL-1 inhibition have been reported. In Table 1 and Table 2, we describe 34 other cases. The majority of cases show a psoriasis flare in patients with pre-existing disease, but a new-onset disease has been reported in 5 cases. Apart from these case reports, 2 publications on adverse events of anti-PD-1 mention psoriasis exacerbation. Danlos et al. [4] report a psoriasis flare in 4 out of 13 patients with psoriasis and Menzies et al. [5] report a flare in 3 out of 6 patients . The number of cases reported suggests that psoriasis exacerbation after ICI may be more common. However, reliable data on the prevalence and incidence of psoriasis in patients treated with anti-PD-1/PDL-1 antibodies are still lacking. In order to detect side effects at an early stage, it is recommended that these side effects of immunotherapy are searched for during each clinical examination. Registration in a systematic way is needed to obtain reliable epidemiologic data. This might also have a predictive value as some retrospective data suggested a better outcome for patients with cutaneous irAEs [6, 7]. At this moment it is unclear whether this is true for psoriasis induced by ICI.

A possible rationale for the pathogenesis can be given but remains speculative. Psoriasis is known as a T-cell- and dendritic-cell-mediated disease. IL-17 and IL-22 produced by T helper (Th) 1, 17, and 22 cells play an important role [8]. Th cells are downregulated by the PD-1 pathway. By inhibiting this pathway, an upregulation of Th-17 cells is observed [9]. Th-17 upregulation might be the explanation why this patient had psoriasis exacerbation parallel to the anti-PD-1 infusion.

The recognition of psoriasis induced by ICI is important for adequate management. General management for skin toxicity of ICI describes the use of topical emollients, antihistamines,

and corticoids [10]. For psoriasis, a more specific approach is needed. Prior recommendations for drug-induced psoriasis were to stop the causal drugs and start classic treatment options for psoriasis vulgaris. These treatment options are currently topical corticosteroids, vitamin D analogues, ultraviolet-based phototherapy, and systemic treatments, such as methotrexate, acitretin, and fumaric acid esters, and biologics [11]. Because of the underlying malignant condition, cyclosporine and many of the novel biologic agents are preferably avoided in patients with PD-1/PDL-1-induced psoriasis unless other severe irAEs are present, e.g., ICI-induced colitis not responding to systemic corticotherapy [3]. Our patient was successfully treated with topical steroids and prolongation of the dosing interval of nivolumab. Indeed, some cases describe good results with topical treatment with corticoids and vitamin D analogues [12–15]. However, in several cases local treatment was insufficient with need for oral prednisolone [2, 16, 17], acitretin (vitamin A derivate), or phototherapy [2, 16, 18, 19]. One patient with concomitant psoriasis arthritis was also treated with oral methotrexate [20]. In most cases, psoriatic lesions were controlled without the need to permanently discontinue the anti-PD-1/PDL-1 therapy; often, only a short break is reported. If psoriasis exacerbation or de novo psoriasis is suspected, we suggest a rapid referral to a dermatologist to initiate a proper local and if needed systemic treatment. With proper treatment, a discontinuation of the ICI can be avoided in most cases.

Conclusion

Psoriasis exacerbation is an established side effect of PD-1/PDL-1 checkpoint inhibitors with 35 reported cases. Early recognition and management are challenging with no clear guidelines available. A close collaboration between oncologist and dermatologist is mandatory to manage this specific irAE.

Statement of Ethics

Written informed consent was obtained from the patient.

Disclosure Statement

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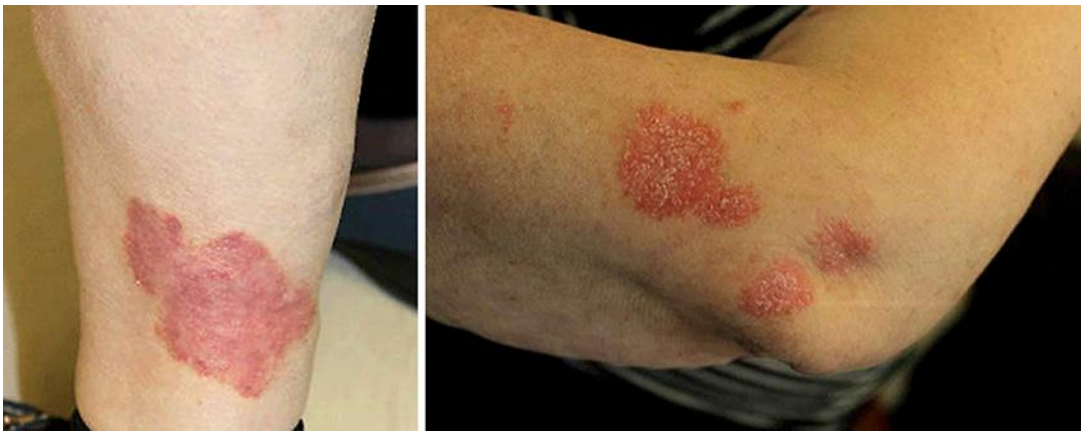

Fig. 1. Psoriatic lesions on both lower and upper limbs.

Table 1. Overview of psoriasis exacerbations and de novo psoriasis in patients treated with anti-PD-1/anti-PDL-1 therapy

Patient age, years/ gender	Cancer type	Treatment regimen	Time between start of PD-1/ PDL-1 inhibitor and appearance of psoriasis	Personal history of psoriasis	Psoriasis management	Discontinuation of PD-1/PDL-1 inhibitor	Tumor response to PD-1/PDL-1 inhibitor	First author [Ref.], year
80/M	Primary oral mucosal melanoma	Nivolumab 2 mg/kg every 3 weeks	12 weeks	No	Oral prednisolone, resulted in therapeutic effect	No	3 months after the last dose of nivolumab, the lesions on the palate decreased in size; no melanoma cells were found in a biopsy taken from the upper lip	Ohtsuka [17], 2015
65/M	Metastatic oral mucosal melanoma	Nivolumab 2 mg/kg every 3 weeks, after subcutaneous interferon-β injections for 5 days	3 weeks	Yes	– Topical steroid (clobetasol propionate 0.05%) and vitamin D3 analogue, without response – UVB therapy, without response – Oral etretinate 30 mg/day, resulted in therapeutic effect	No	NA	Kato [16], 2015
45/M	Metastatic renal cell carcinoma	Nivolumab 3 mg/kg every 2 weeks	2 weeks	No	Calcipotriol/ betamethasone gel, resulted in therapeutic effect	Yes; interruption of 21 days	Partial response on CT scan	Ruiz-Bañobre [13], 2017
87/M	Metastatic cutaneous melanoma	Nivolumab 2 mg/kg every 3 weeks	6 weeks	Yes	Systemic corticoids (0.5 mg/kg), resulted in therapeutic effect	Yes; interruption because of concomitant pneumonitis	NA	Matsumura [9], 2015
80/F	Metastatic cutaneous melanoma	Pembrolizumab	Between 3 and 6 weeks	NA	Local corticoids	Yes	Yes	Totonchy [15], 2016
67/M	Metastatic adenocarci-noma of the lung	Pembrolizumab	3 weeks	Yes	Acitretin	Yes; interruption of 4 weeks	NA	Sahuquillo-Torralba [19], 2016
NA	NA	Pembrolizumab	9 weeks	Yes	Topical and systemic corticoids	Yes; interruption of 1 week	NA	Sanlorenzo [21], 2015

NA, not applicable.

Table 2. Overview of psoriasis exacerbations and de novo psoriasis in patients treated with anti-PD-1/anti-PDL-1 therapy (continued)

Patient age, years/ gender	Cancer type	Treatment regimen	Time between start of PD-1/ PDL-1 inhibitor and appearance of psoriasis	Personal history of psoriasis	Psoriasis management	Discontinuation of PD-1/PDL-1 inhibitor	Tumor response to PD-1/PDL-1 inhibitor	First author [Ref.], year
17 patients: age 35–87 years/ F/M	Melanoma/ lung carcinoma	Pembrolizumab/ nivolumab	NA	NA	Topical, systemic corticosteroids, acitretin, phototherapy	NA	NA	Bonigen [2], 2017
67/M	Advanced non-small cell lung cancer	Nivolumab 3 mg/kg every 3 weeks	3 weeks	No	Topical corticoids, resulted in therapeutic effect	No	NA	Yamamoto [14], 2018
67/M	Stage IV melanoma	Pembrolizumab 2 mg/kg every 3 weeks	15 weeks	Yes	Acitretin and narrow band ultraviolet B phototherapy	Yes; interruption of 4 weeks	Yes	Phadke [18], 2016
5 patients: mean age 66 years/ F/M	3 NSCLC, 1 papillary urothelial carcinoma, 1 squamous cell carcinoma of the tonsil	3 patients treated with anti-PD-1 therapy (1 with pembrolizumab, 2 with nivolumab) 2 patients treated with anti-PDL-1 therapy (durvalumab)	Between 2 weeks and 2 months	In 3 out of 5 patients the personal history was positive for psoriasis	Topical steroids, ultraviolet B phototherapy, systemic steroids	In 1 out of 5 patients therapy was interrupted	NA	Voudouri [3], 2017
89/M	Metastatic melanoma	Nivolumab 3 mg/kg every 2 weeks	2 weeks	No	Calcipotriol/ betamethasone dipropionate (local)	No	No	Murata [12], 2017
80/M	NSCLC	Nivolumab 3 mg/kg every 2 weeks	16 weeks	No	Oral methotrexate at a dose of 10 mg/ week in combination with low-dose 15 mg oral prednisone/ day and topical corticosteroids	Yes; interruption of 4 weeks	Yes	Law-Pingman [20], 2016
65/F	Metastatic melanoma	Nivolumab 3 mg/kg every 2 weeks	20 weeks	Yes	Topical corticosteroids, prolongation of treatment interval to 3 weeks	Yes; nivolumab every 3 weeks instead of every 2 weeks	Yes	Our case

NA, not applicable.