A case of de novo palmoplantar psoriasis with psoriatic arthritis and autoimmune hypothyroidism after receiving nivolumab therapy

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Abstract

Nivolumab, a monoclonal antibody against the programmed cell death protein 1 (PD-1), has shown promising results in patients with advanced malignancies, including melanoma, lung cancer, and renal cancer. Immune-related adverse events (irAEs) have been reported, including both organ-specific toxicities and skin toxicities. Herein, we report a case of predominantly palmoplantar psoriasis with severe nail involvement, psoriatic arthritis, and autoimmune hypothyroidism after receiving nivolumab treatment for lung cancer. We also summarize the case reports that have been published previously. The knowledge of these irAEs in patients undergoing anti-PD1 therapy is important since it will enable earlier recognition and appropriate management, with the aim of maintaining effective dose without disruption.

Keywords: nivolumab, psoriasis, arthritis, anti-PD-1, autoimmune hypothyroidism

Introduction

Anti- programmed cell death protein 1 (PD-1) immunotherapy blocks the interaction between PD-1 and PD ligand-1, stimulating T-cell activity and helping the anticancer host immune response [1]. Nivolumab has been approved for advanced melanoma, metastatic non-small cell lung cancer, and renal cell carcinoma. We report a case of predominantly palmoplantar psoriasis, psoriatic arthritis, and autoimmune hypothyroidism after receiving nivolumab treatment for lung cancer.

Case Synopsis

A 68-year-old man was referred to our hospital for treatment of metastatic non-small cell lung cancer. He did not have any personal or family history of psoriasis, rheumatic disease, or endocrine disease. The patient began nivolumab at the dose of 3mg/kg every 2 weeks, after failure of previous treatment with carboplatin/paclitaxel and pemetrexed. After the third infusion, he developed well demarcated erythema and severe hyperkeratosis affecting his entire palms and soles (**Figure 1**) He also exhibited isolated sharply bordered, scaly erythematous plaques on the trunk and extremities. Furthermore, he had subungual hyperkeratosis, onycholysis, and salmon patches affecting every nail (**Figure 2**). Treatment with topical corticosteroid (clobetasol propionate 0.05%) and oral prednisone (30 mg daily) was initiated.

A skin biopsy from the hand was performed. It showed parakeratosis with regular acanthosis, dilated blood vessels in the papillary dermis, and perivascular lymphocytic infiltration and neutrophils in the cornified layer, confirming the diagnosis of psoriasis. Moreover, the patient developed severe pain in the extremities with tenderness and swelling of the right wrist, right knee, and ankles. Aspiration of the knee showed a synovial fluid with inflammatory characteristics; a diagnosis of psoriatic arthritis was made. There was no evidence of established erosive disease on X-ray evaluation. A blood test revealed reduction of thyroxine (0.25 ng/dl), elevation of thyroid-stimulating hormone (31.07 µu/ml), and the presence of antithyroid microsomal antibodies. No other abnormalities were found,

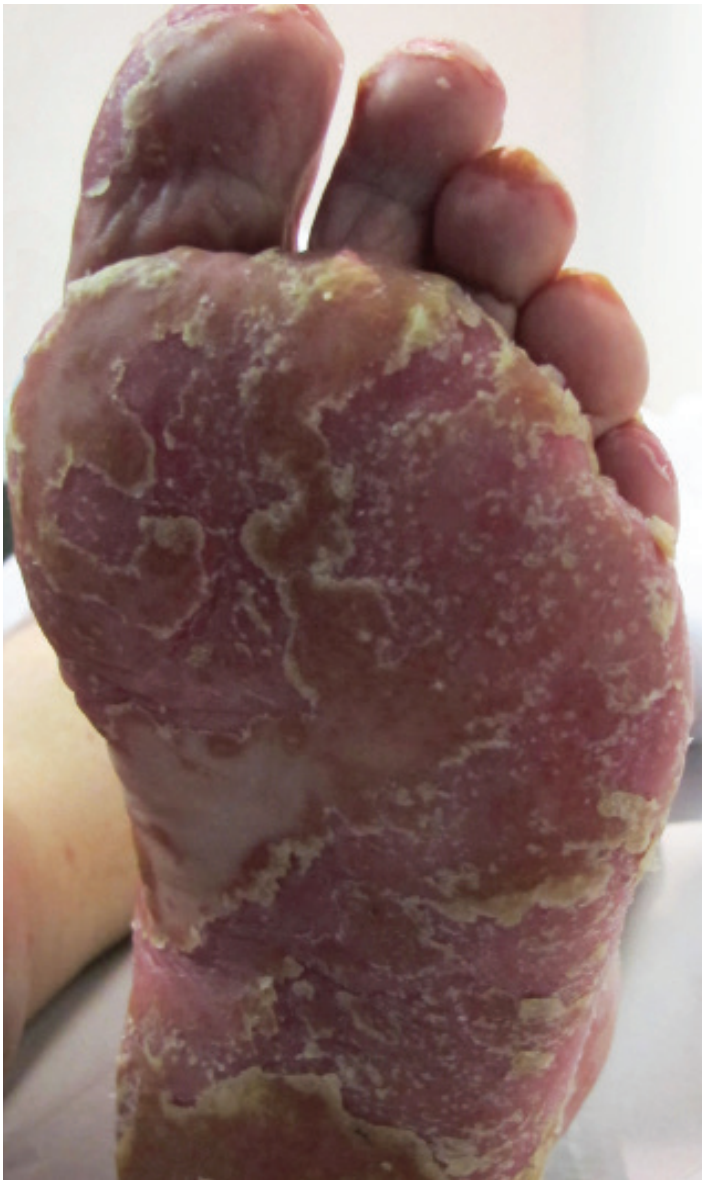

Figure 1. *Well demarcated erythema and surface scaling with intense hyperkeratosis affecting the entire left sole.*

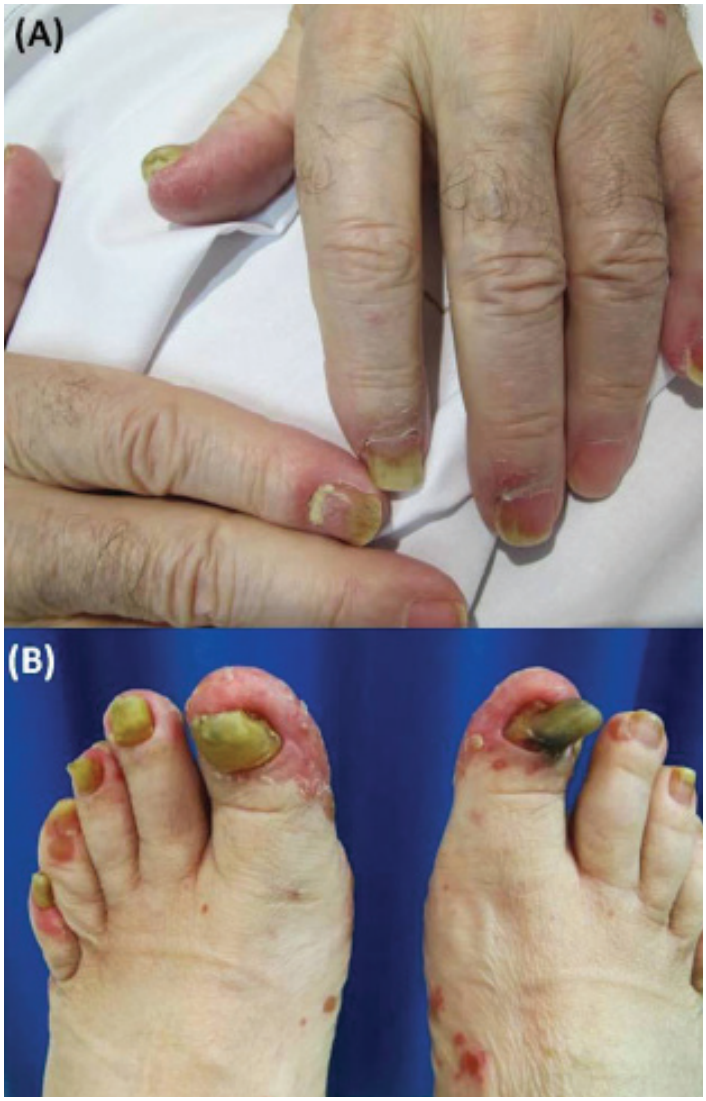

Figure 2. *A) Subungueal hyperkeratosis, onycholysis and salmon patches affecting every nail of the hands. B) Similar nail affectation on the feet.*

including serum antibody tests for RF, anti-CCP, ANA, HLA-B27, and serologies for HBC, HBV, and HIV. De novo palmoplantar psoriasis with psoriatic arthritis and autoimmune hypothyroidism triggered by nivolumab therapy was diagnosed. Nivolumab was discontinued and oral metotrexate (10mg/week) with a tapering dose of oral prednisone (10mg/day) were introduced. A computed tomography (CT) scan revealed a marked regression of the mass. After 9 months of therapy, both skin lesions and joint symptoms gradually resolved, but the CT scan showed progression of the lung cancer. Nivolumab was not restarted owing to the severity of the side-effect (grade 3 toxicity). He has recently started carboplatin/gemcitabine combination therapy.

Case Discussion

Anti-PD-1 immunotherapy is generally well tolerated, but adverse events have been observed in more than 80% of all patients, mostly related to an augmented immune response. Immune-related adverse events (irAEs) have been reported, either organ-specific toxicities (colitis, hypophysitis, and thyroiditis) or skin toxicities. The most frequent irAEs in the skin are lichenoid reactions, vitiligo, and eczema [2].

Recently, a few case reports of exacerbation or occurrence of psoriasis have been reported with anti-PD-1 therapies (**Table 1**), [2-10]. Previous studies have demonstrated that blockade of PD-1 by its antibodies, augmented the Th1 and Th17 responses in patients with advanced cancer, which might

Table 1. Case reports of exacerbation or occurrence of psoriasis which have been reported with nivolumab and pembrolizumab therapies

	CASE	Sex / Age (y)	Previous history of psoriasis	Cancer type	Anti-PD-1	Nº of doses	Clinical type	Palmo-plantar	Other adverse events	Treatment	Evolution of the cancer
1	Ohtsuka et al., 2015. [2]	M, 80	No	Melanoma	Nivolumab	4	Plaque	No	Systemic symptoms (fever, pain of the extremities)	Oral prednisolone (0,7mg/kg)	Improved
2	Kato et al., 2016. [3]	M, 65	Yes	Melanoma	Nivolumab	1	Plaque	No	None	Oral etretinate (30mg/d)	No information
3	Matsumura et al., 2016. [4]	M, 87	Yes	Melanoma	Nivolumab	2	Plaque	No	Interstitial pneumonia	Oral prednisolone (0,5mg/kg)	Improved
4	Sahuquillo-Torralba et al., 2016. [5]	M, 67	Yes	Lung cancer	Pembrolizumab	1	Erythrodermia	Yes	None	Acitetrin (35mg/d)	Improved
5	Murata et al., 2017. [6]	M, 89	No	Melanoma	Nivolumab	1	Plaque	No	Vitiligo	Calcipotriol/betamethasone dipropionate combination ointment	Worsened[a]
6	Law-Ping-Man et al., 2016. [7]	M, 80	No	Lung cancer	Nivolumab	8	Plaque/scalp	No	Psoriatic arthritis	Metotrexate (10mg/d) + prednisone (15mg/d) + topical corticosteroids	Improved
7	Schmutz JL, 2016. [8]	M, 80	No	Lung cancer	Nivolumab	8	No information	No	Psoriatic arthritis	Metotrexate + prednisone	Improved
8	Totonchy et al., 2016. [9]	F, 80	No	Melanoma	Pembrolizumab	2	Inverse	No	None	Clobetasol (0.05%) + mupirocin ointments	Improved
9	Ruiz-Bañobre et al., 2017. [10]	M, 45	No	Renal cell carcinoma	Nivolumab	1	Plaque	No	None	Calcipotriol/betamethasone	Improved
10	Our case	M, 68	No	Lung cancer	Nivolumab	3	Palmoplantar/ Nail	Yes	Psoriatic arthritis + autoimmune hypothyroidism	Metotrexate (10mg/d) + prednisone (30mg/d) + topical corticosteroids	Improved[b]

M, Male; F, Female

a, Case 5, the patient died 6 months after initiating nivolumab therapy, of melanoma-related disseminated intravascular coagulation

b, Case 9, the patient had marked partial response with nivolumab, but the disease progressed when nivolumab therapy was stopped.

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correlate with antitumor effect [2]. IL-17, the principal effector cytokine of Th17 cells, plays a key role in the pathogenesis of both psoriasis and psoriatic arthritis. Thus, a psoriatic eruption in patients receiving nivolumab treatment may be a consequence of the PD-1 blockade [3].

Conclusion

Immune checkpoint inhibitors have demonstrated improved survival in patients with certain malignancies and are now widely used in clinical practice. The recognition of these irAEs in patients undergoing anti-PD1 therapy is extremely important since it will enable earlier recognition and appropriate management, with the aim of maintaining an effective dose without disruption.

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