Severe de-novo palmoplantar and nail psoriasis complicating Nivolumab treatment for metastatic melanoma

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Running head: psoriasis complicating nivolumab treatment.

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Abstract

Immunotherapy with nivolumab has shown durable disease control and tumor regression in advanced melanoma, metastatic non-small cell lung cancer, renal carcinoma, Hodgkin's lymphoma, squamous cell carcinoma of the head and neck and urothelial carcinoma. Since PD-1 receptor plays an important role in promoting self-tolerance by the down-modulation of T-cell activity, deregulation of immune tolerance caused by nivolumab may determine immune-related adverse events (irAEv). Among irAEs by nivolumab, skin toxicities represent the most common. In recent years more and more cases of psoriasis exacerbation and new-onset psoriasis during anti-PD-1 treatment have been reported in the literature. To date, only one case of *de-novo* palmoplantar and nail psoriasis after receiving nivolumab therapy has been described so far. We report a case of severe new-onset palmoplantar and nail psoriasis after receiving nivolumab treatment for advanced melanoma. Our case highlights the importance of prompt recognition and adequate management of the immunotherapy-associated psoriasiform eruptions, which can worsen the quality of life and lead to suspension of potentially life-saving medication.

Introduction

Nivolumab, a fully human IgG4 immune checkpoint modulator, binds to the programmed cell death 1 (PD-1) receptor on T cells and blocks their inhibition. Thus, it increases the anticancer host immune response by allowing T cells to attack tumor cells. Immunotherapy with nivolumab has been successfully used for the treatment of advanced melanoma, metastatic non-small cell lung cancer, renal carcinoma, Hodgkin's lymphoma, squamous cell carcinoma of the head and neck and urothelial carcinoma. Although anti-PD-1 immunotherapy is typically well

accepted, adverse events affect more than 80% of all patients. Since PD-1 receptor plays an important role in promoting self-tolerance by the down-modulation of T-cell activity, deregulation of immune tolerance caused by nivolumab may determine immune-related adverse events (irAEv). Among irAEs by nivolumab, skin toxicities represent the most common. They are usually of mild entity and often consist in maculopapular rash, pruritus, vitiligo and eczema. However, severe cutaneous reactions are possible [1-3].

Case

A 59-year-old man with metastatic melanoma was commenced on nivolumab 3 mg/kg every 2 weeks in November 2017. The patient had a personal history of B-raf negative melanoma of the thorax with Breslow thickness (BT) of 3.1 mm, excised one year before. He had undergone surgical enlargement and sentinel lymph node biopsy of the neck nodes had resulted negative. However, during follow-up, there had been instrumental evidence of hepatic recurrences and adjuvant nivolumab was started.

During the first four months of nivolumab therapy, the patient gradually but rapidly developed painful hyperkeratosis and fissuring on the plants. Moreover, both fingernails and toenails became thicker, brown-black in color and painful. The patient did not have any personal or family history of skin/adnexal disease, whereas he suffered from hypertension and depression. Because of the presumed severe skin toxicity related to nivolumab, his oncologist decided to discontinue nivolumab therapy and prescribed an emollient cream to be applied on both skin and nails. However, 20 days after ceasing nivolumab, no much benefit was noted. Therefore, the patient was referred to our Outpatient Consultation for Nail Disease of the Dermatology Unit of the Department of Experimental, Diagnostic and Specialty Medicine (DIMES) of the University of Bologna for the management of his cutaneous and nail abnormalities.

On physical examination, well demarcated erythematous-squamous plaques were observed on both soles, more prominent on pressure areas. Conversely, the palms were spared. Marked subungual hyperkeratosis with nail thickening, brown-black nail discoloration associated with painful periungual inflammation were evident in toenails and fingernail, more marked on the fingernails (Fig. 1). No other skin lesions were observed. No significant changes were noted on blood tests compared to the patient's previous results. A longitudinal nail biopsy from a toenail and a skin biopsy from the plantar region were performed. Histology confirmed the clinical suspicion. In particular, histopathological examination of the nail material showed hyperkeratosis with focal parakeratosis, mostly neutrophilic infiltrate, a spongiotic pustule, serum exudates, hyperplasia of the nail bed epithelium and dilated vessels in the dermis. Moreover, granulosis in the nail matrix was present. Sole biopsy showed severe epidermal psoriasiform hyperplasia, parakeratosis, neutrophilic collection in the epidermis and corneum layer. Neutrophils and dilated vessels were also observed in the superficial dermis (Fig. 2).

The overall picture and the patient's history suggested *de novo* severe palmoplantar and nail psoriasis triggered by nivolumab therapy. Topical therapy was prescribed as follows: clobetasole propionate 0,05% solution to be applied twice daily on the periungual tissues, using an eyeshadow brush, and 50% urea gel to be applied on the nail plates overnight. Plantar psoriasis was treated with clobetasole propionate 0,05% cream once a day.

Systemic therapy with nivolumab was re-started. Over the following months, despite the resumption of nivolumab, psoriatic cutaneous lesions completely disappeared and marked nail improvement was observed, with disappearance of the periungual inflammation and marked thinning of the nail plate. At the 12-month follow-up, the malignancy was stable and no evidence of disease progression was observed. Moreover, no further nail or cutaneous abnormalities were detected.

Discussion

In recent years more and more cases of psoriasis exacerbation and new-onset psoriasis during anti-PD1 therapy have been reported in the literature [3-6]. To date, only one case of *de-novo* palmoplantar and nail psoriasis after receiving nivolumab therapy has been described so far.[3]

In case of immunotherapy with nivolumab, clinicians should search for cutaneous and adnexal side effects during each clinical examination, since palmoplantar and nail psoriasis are within the spectrum of toxicity of this drug. The biologic mechanism underlying the development of nivolumab-induced palmoplantar and nail psoriasis is yet to be determined. However, some authors have postulated that psoriatic reactions complicating anti-PD-1 therapy may be the consequence of PD-1 blockade by its antibodies. Indeed, psoriasis is a chronic multifactorial T-cell-mediated disease, where IL-17 plays a key role in the pathogenesis. The cells that mainly produce this cytokine (T-helper 1 and 17) are downregulated by the PD-1 pathway. Therefore, we can speculate that, on one hand, the increased Th1 and TH17 response induced by nivolumab plays an antitumor effect in patients with advanced cancer and, on the other hand, this increased Th1 and TH17 response may unmask a psoriatic reaction in a predisposed individual. Moreover, PD-1 receptor promotes self-tolerance by the down-modulation of T-cell activity. Therefore, nivolumab therapy may unmask an immune response by blocking PD-1 on T-cells and deregulating immune tolerance to pre-existing self-antigens located at specific body regions [4,6].

To the best of our knowledge, this is the second reported case of palmoplantar and nail psoriasis after nivolumab treatment. In our opinion, histological examination should be always performed in these cases to make a diagnosis of certainty and justify the subsequent therapeutic choices. In our case, nail and skin psoriasis induced by nivolumab were successfully treated with topical high potency corticosteroids. Forty per cent urea keratolytic gel applied on the nail

plates was useful to reduce hyperkeratosis and allow an increased drug penetration. Moreover, there was no need to suspend or prolong the dosing interval of nivolumab.

In the previously reported case of *de novo* palmoplantar and nail psoriasis associated with psoriatic arthritis and autoimmune hypothyroidism occurring in a patient undergoing nivolumab treatment for a metastatic non-small cell lung cancer, nivolumab was discontinued and oral methotrexate and prednisone were introduced. That patient had a gradual resolution of skin lesions and joint symptoms after 9 months of therapy, but his lung cancer progressed when nivolumab was stopped [3].

Therefore, in case of nivolumab-induced palmoplantar and/or nail psoriasis the suggestion is not to permanently or even temporarily suspend nivolumab treatment, but to ask for an immediate dermatologic consultation and promote the use of topical therapy for the skin lesions. Indeed, in predisposed patients, palmoplantar and nail psoriasis is only triggered but not caused by nivolumab and does not subside after drug discontinuation.

Our case highlights the importance of prompt recognition and adequate management of the immunotherapy-associated psoriasiform eruptions, which can worsen the quality of life and lead to suspension of potentially life-saving medication. We believe that severe palmoplantar and nail psoriasiform toxicity does not always require discontinuation of nivolumab therapy, since it may be properly controlled using topical corticosteroids. More aggressive systemic drugs should be avoided as much as possible because of the underlying metabolic problems related to the tumor.

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Figure legend

Fig. 1. Clinical pictures of nail and skin lesions after four months from the start of nivolumab therapy. A) Thickened fingernails with marked subungual hyperkeratosis, brown-black discoloration and periungual inflammation; b) thickened toenails with subungual hyperkeratosis; c) well demarcated erythematous-squamous plaques on the left sole, more prominent on pressure areas.

Fig. 2. Histological pictures of nail and skin lesions after four months from the start of nivolumab therapy. a) Nail matrix epithelium hyperplasia and granulosis. A spongiotic pustule is also visible. H&E 2X; b) epidermal hyperplasia, parakeratosis, absence of granulous layer,

collection of neutrophils in the epidermis of the plantar lesion; neutrophils and dilated vessels are visible in the superficial dermis. H&E 12X.