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Letter to the Editor

Successful treatment of psoriasis induced by immune checkpoint inhibitors with apremilast

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To the Editor

The use of immune checkpoint inhibitors (ICIs) has hugely incremented as it has become the standard therapy for a wide range of cancer types. Such monoclonal antibodies act against inhibitory immune receptors cytotoxic T-lymphocyte antigen 4 (CTLA-4) (ipilimumab and tremelimumab) and programmed cell death 1 (PD-1) (nivolumab and pembrolizumab) by boosting the immune response of T cells [1]. Despite favourable oncological outcomes, these treatments have also been associated with a unique spectrum of side-effects known as immune-related adverse events (irAEs) [2]. The most common cutaneous irAEs are maculopapular rashes, pruritus, vitiligo and psoriasis, but other uncommon auto-immune skin diseases such as bullous pemphigoid and dermatomyositis are also possible [3]. Among the various toxicities, onset or exacerbation of psoriasis makes management of patients with cancer difficult due to the limited therapeutic possibilities and the strong impact on the quality of life. We report the first case of psoriasis triggered by nivolumab therapy successfully treated with apremilast in a patient with non–small-cell lung cancer (NSCLC).

1. Case report

A 74-year-old woman presented with multiple well-demarcated, raised, red plaque with a white scaly surface varying in size from 1 to 6 cm, some of which were excoriated on both lower and upper limbs (Fig. 1) to our outpatient department for oncological patients. In addition, psoriasiform scales on the scalp and retroauricular area were observed. She complained of intense itching with important impairment of the quality of life. The patient had a known history of psoriasis (in remission for several years), hypercholesterolaemia, hypertriglyceridemia and hypertension. Six months before presentation, the patient started a treatment with nivolumab (3 mg/kg every 2 weeks) for a non-metastatic

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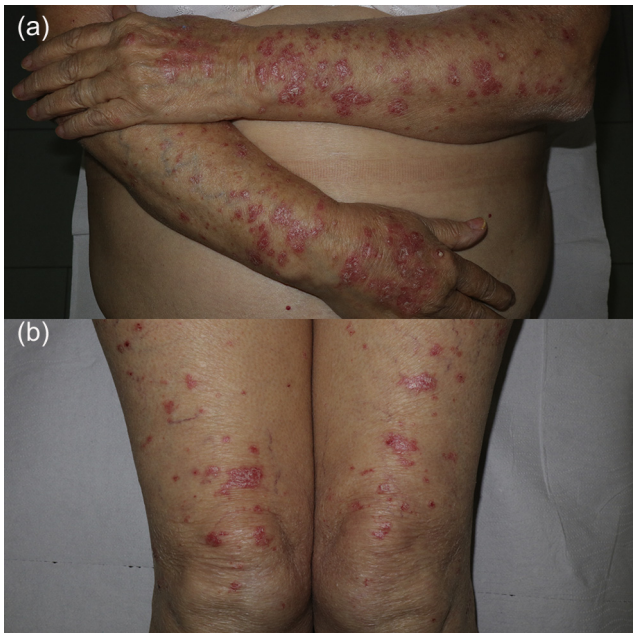

Fig. 1. Numerous well-demarcated, raised, red plaques with a white scaly surface on both upper (a) and lower limbs (b). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

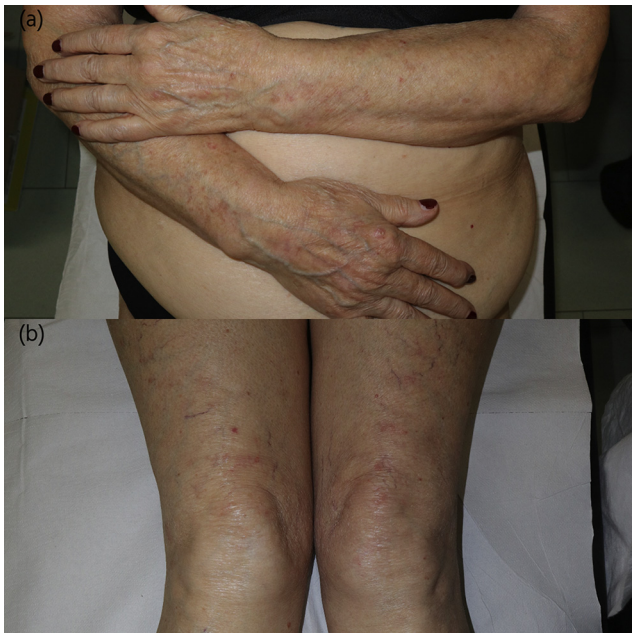

Fig. 2. Clinical improvement after 6 weeks of therapy on both upper (a) and lower limbs (b).

non–small-cell lung cancer. The diagnosis of psoriasis vulgaris exacerbation was made clinically, and a biopsy specimen was not obtained. Over the next 2 weeks, the skin condition progressively worsened despite the use of calcipotriene and betamethasone dipropionate foam and emollients. Therapy with acitretin and methotrexate was contraindicated for dyslipidemia and pulmonary condition, respectively, and patient refused to undergo phototherapy. Because of the strong discomfort experienced by the patient, we decided to use apremilast under strict dermatological and oncological control with standard titration dosing schedule (10 mg on day 1 and increasing the dose by 10 mg daily), until reaching a maintenance dose of 30 mg twice daily on day 6. Although she initially experienced nausea, apremilast was well tolerated. Over the next 6 weeks, she had a remarkable clinical improvement with reduction of pruritus, disappearance of the skin patches and better quality of life, without any obvious interference with immunotherapy (Fig. 2).

2. Discussion

The risk of developing psoriasis with ICIs is known even though reliable data on its prevalence and incidence are still lacking. Most cases show a psoriasis eruption in patients with pre-existing disease, but a new-outbreak disease has been reported [4]. The pathogenesis has not been clarified. Psoriasis is a chronic, immune-mediated disorder with cutaneous and systemic manifestations and substantial negative effects on a patient's quality of life. It is considered to be mediated by cytotoxic T cells and more specifically by T helper (Th1) and Th17-cells. Interleukin (IL)-17 and IL-22 produced by Th 1, 17 and 22 cells play an important role [5]. T-cell activation induced by immunotherapeutic agents, with the contribution of other triggers, facilitates the psoriasis onset/worsening in patients with personal or family history. It has been observed that the PD-1 axis downregulates Th1/Th17 signalling pathway [6]. By inhibiting this pathway, an upregulation of Th17 lymphocytes with secondary overexpression of proinflammatory cytokines is observed [7]. Th17 upregulation could be the cause of this patient's psoriasis exacerbation during the anti–PD-1 administration.

Appearance or exacerbation of psoriasis in a patient with cancer can be catastrophic because the patient is already physically and psychologically debilitated by the cancer and there are very few weapons available for dermatologists to counter this type of toxicity during immunotherapy.

In most cases, the eruption can be controlled with topical treatments, steroids and/or vitamin D analogues, and immunotherapy can be maintained. Acitretin or methotrexate could be taken into account in resistant psoriasis. Phototherapy can also be valuable but should be assessed for patients with melanoma because of photo-induced skin carcinogenesis. In addition, patients with cancer are often unable to go to the hospital several times a week and stay upright during the session. Moreover, cyclosporine and many of the novel biologic agents are preferably avoided in patients with PD-1/

PDL-1–induced psoriasis because cancer is a contraindication for these treatments [8]. There are no data available regarding the efficacy and safety of small molecules (as well as biologics) used for treatment of psoriasis in patients with malignancies. Apremilast is a phosphodiesterase-4 (PDE-4) inhibitor that increases intracellular cyclic adenosine monophosphate (cAMP) levels in immune cells through protein kinase A (PKA) phosphorylation and activation, resulting in upregulation by cAMP-responsive element–binding protein (CREB) and down regulation of nuclear factor kappa B (NF-κB)–dependent genes. Consequently, production of cytokines and chemokines such as tumour necrosis factor alpha, interferon gamma, IL-12 and IL-23, CXCL9, CXCL10 and CCL4 decreases with an increasing production of anti-inflammatory mediators such as IL-10 [9]. Despite an inhibitory effect on Th1, Th2 and Th17 cytokine production, apremilast did not have any effect on T-cell or B-cell clonal enlargement or on antibody functions. These results may explain the low risk of infection and the general safety profile reported in clinical studies so far [10]. Therefore, apremilast appears to predominantly affect innate immunity and is not contraindicated in patients with malignancy.

To our knowledge, this is the first reported case of apremilast for the treatment of psoriasis induced by nivolumab. The impact of apremilast on immunotherapy efficacy is uncertain. However, as recently noted, administration of systemic corticosteroids or other immune-modulating drugs in patients treated with anti–PD-1 agents does not seem to affect the anticancer immune response [11].

Apremilast can be a potentially effective and safe option for the treatment of psoriasis induced by ICIs. In case of psoriasis worsening or suspected de novo psoriasis, we recommend a timely dermatological consult. An appropriate treatment, in most cases, can prevent a discontinuation of the ICI.

Conflict of interest statement

None declared.

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None.

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