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DERMATOLOGIC THERAPY WILEY

LETTER

Successful treatment with apremilast of severe psoriasis exacerbation during nivolumab therapy for metastatic melanoma

Dear Editor,

Psoriasis is a chronic, immune-mediated, systemic, inflammatory disease with prominent skin manifestations affecting quality of life. Worsening and recurrence of psoriasis have been reported in patients affected by metastatic melanoma during the use of Immune checkpoint inhibitor, both anti-CTLA4 and anti-PD-1, such as nivolumab.[1-3] We report the case of a patient with metastatic melanoma and severe exacerbation of psoriasis by nivolumab, successfully treated with apremilast.

In February 2015 a 62-year-old male patient with personal psoriasis history underwent surgical resection of melanoma of the left buttock histologically characterized by nodular features, ulceration, Breslow thickness of 9 mm, 12 mitoses/mm^2, Clark level IV, in presence of modest intratumoral and peritumoral lymphocytic infiltrate. According to the negativity of sentinel lymph node biopsy, patient was staged as pT2c. In July 2015, positron-emission tomography (PET scan) showed pathological enhancement of the retroperitoneal and left inguinal lymph nodes (standardized uptake values from 2.6 to 22.5). He underwent complete lymph node dissection (CLND), resulting in 23 out of 42 metastatic lymph nodes. The PET scan completed 2 months later demonstrated residual disease in the retroperitoneal lymph nodes. Based on mutational status revealing the NRAS mutation, the patient started first line treatment with ipilimumab that was considered the best option notwithstanding the history of psoriasis. The patient developed acute hemorrhagic colitis after the third dose of ipilimumab that was successfully treated with high-dose of steroids followed by Infliximab. Two months after the discontinuation of ipilimumab, TC scan revealed progression and the patient started nivolumab (240 mg/month). About 3 weeks after the first course of nivolumab treatment, severe psoriasis exacerbation developed on the trunk and limbs with sharply bordered, scaly, and erythematous plaques (Figure 1). A skin biopsy showed parakeratosis, perivascular lymphocytic infiltration, slight elongation of rete ridges, dilated vessels in the papillary dermis, thinning of the granular layer, and neutrophils in the cornified layer. Nivolumab therapy was continued and despite treatment with a betamethasone and calcitriol ointment the skin eruption worsened (PASI 44, DLQI 20). Apremilast was started (30 mg twice daily, after the induction) and 3 months later we observed a slight improvement of psoriasis (PASI 35, DLQI 6). After 6 months of treatment, lesions continued to improve (PASI 21, DLQI 4) and at 12-month follow-up the patient reported only minor flare-ups (PASI 5, DLQI 0) (Figure 2), achieving PASI 90. Of note, nivolumab treatment did not show any toxicity, and apremilast was well tolerated and apparently not associated with worsening of melanoma. After 42 months of therapy with nivolumab and apremilast, diseases were stable.

Psoriasis or psoriasiform eruption is well known to occur as a paradoxical reaction during biological therapies for severe psoriasis.[4] Among these cases, the authors used topical steroids and calcitriol, methotrexate and cyclosporine to control the skin symptoms. This phenomenon is thought to be mediated by the increased production of interferons.[4] Previous studies have demonstrated that blockade of the immune-checkpoint receptors, such as PD-1 and cytotoxic T-lymphocyte antigen-4, by its antibodies augmented the helper T cell type 1 (TH1) and TH17 cell activities, which might correlate with antitumor effect.[5,6] In our case, we could hypothesize that nivolumab may have canceled this suppression, exacerbating psoriasis.

Apremilast is an orally administered small molecule that specifically inhibits the phosphodiesterase-4 enzyme and modulates the immune

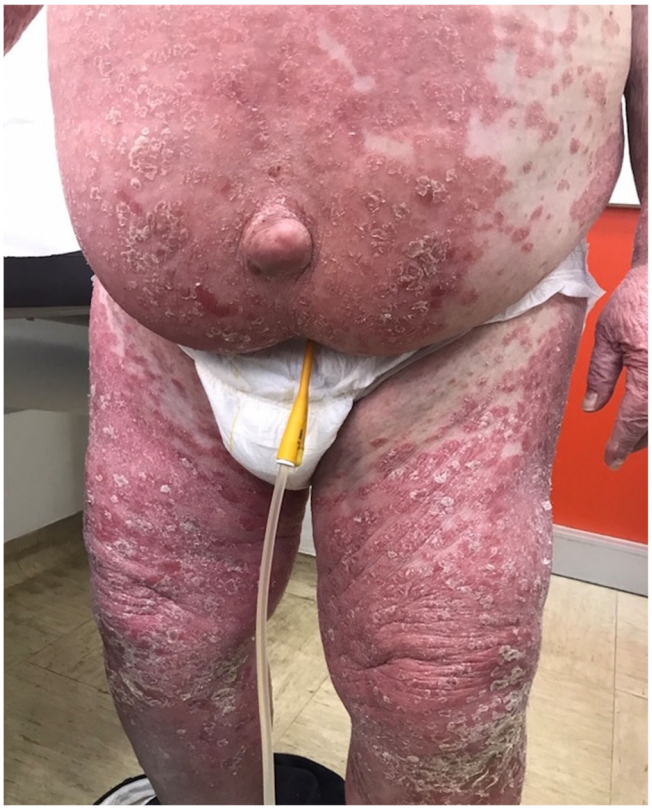

FIGURE 1 Severe psoriasis exacerbation developed about 3 weeks after the first course of nivolumab treatment (PASI 44)

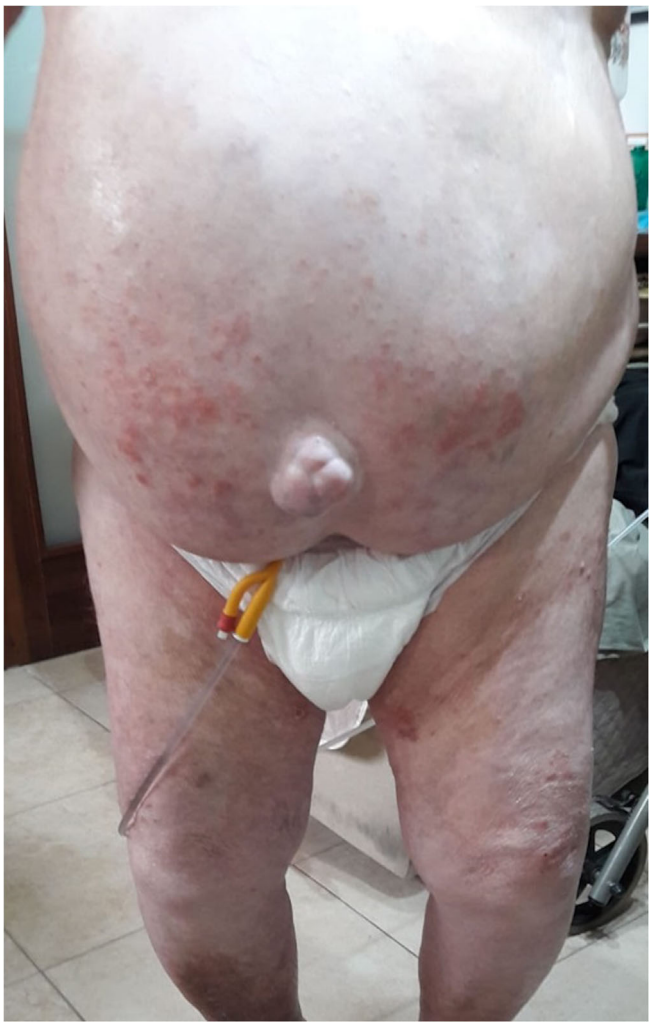

FIGURE 2 About 12-month follow-up: almost complete remission of psoriasis with apremilast treatment

system by increasing the levels of intracellular cyclic adenosine monophosphate (cAMP) and inhibiting IL-2 and IL-8, interferon-γ, and tumor necrosis factor (TNF) production. It is approved for the treatment of psoriasis, psoriatic arthritis, and oral ulcers of Behcet's disease.

Compared with cyclosporine, methotrexate, and biologic drugs, apremilast lacks the immunosuppressive activity that can be associated with increased risk for malignancy or infection. Hence, apremilast has a relatively good safety profile and may be a suggested treatment option for patients with recent or ongoing cancer, also in therapy with immune checkpoint inhibitor drugs.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Caterina Foti, Marco Tucci, Lucia Lospalluti, Rosa Frisario and Paolo Romita: Managed the patient and prepared the manuscript with critical input and revisions from Caterina Foti, Luca Stingeni, Katharina Hansel, Roberta Giuffrida and Paolo Romita.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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