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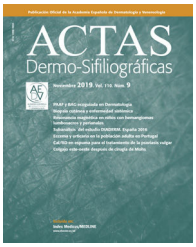

CASE AND RESEARCH LETTER

[Translated article] Psoriasis and Anti-PD-1 and Anti-PD-L1 Immunotherapy: Three Cases, a Review of the Literature, and a Proposed Management Algorithm

Psoriasis y anti-PD1/anti-PDL1: presentación de tres casos, revisión de la literatura y propuesta de algoritmo de manejo

To the Editor,

Anti-PD1 and anti-PDL1 immune checkpoint inhibitors constitute a new, efficacious therapeutic weapon in the treatment of cancer. Nevertheless, these drugs produce immune-related adverse effects, inherent to their antitumor mechanism of action, which often involve the skin and can lead to their withdrawal. Dermatologic toxicity due to anti-PD1 and anti-PDL1 may manifest in highly varied ways, including psoriasis.[1] The pathogenesis of psoriasis induced by anti-PD1 and anti-PDL1 appears to be attributed to an overactivation of Th1, Th17, and Th22 lymphocytes secondary to inactivation of the PD1 immunomodulatory pathway.[2]

In our hospital, we assessed 3 patients who developed psoriasis as a result of treatment with anti-PD1 and anti-PDL1 for gallbladder cancer, cancer of the larynx, and a metastatic melanoma (Fig. 1). We also performed a search of the literature for published cases of psoriasis due to anti-PD1 and anti-PDL1 and we recorded the following variables: age, sex, type of tumor, type of anti-PD1/PDL1, dosage regimen used, time to appearance of lesions, personal history of psoriasis, treatment administered, interruption of treatment with anti-PD1/PDL1, and response of tumor to immunotherapy. Finally, we propose an algorithm for the treatment of psoriasis induced by anti-PD1 and anti-PDL1.

Our patients and the cases published in the literature account for 43 cases of psoriasis induced or exacerbated by anti-PD1 (26 by nivolumab and 12 by pembrolizumab) and anti-PDL1 (3 by atezolizumab and 2 by durvalumab) (Table 1).[3–7] The mean age of the patients was 65.7 years (35–87 y), with a predominance of males (34/43, 79%). The most frequent types of neoplasia were melanoma and lung cancer, which together accounted for 18 out of 43 cases (41.9%), followed by urothelial carcinoma (3/43, 7%), renal cell carcinoma, diffuse large B cell lymphoma, tonsil cancer, and squamous cell carcinoma of the larynx (1 case out of 43 each, 2.3%). The mean time from instatement of immunotherapy to appearance of the psoriasis lesions was 9.6 weeks. Eleven of the 43 cases stated that they had no personal history of psoriasis (25.6%) and 14 of the 43 presented an exacerbation of their previous psoriasis with anti-PD1/anti-PDL1 treatment (32.6%), although this information was not recorded in many of the published studies. In nearly half of patients, the psoriasis was managed with topical treatment alone (20/43, 46.5%). The most commonly used systemic therapies were oral retinoids (9/43, 20.9%), phototherapy and systemic corticosteroids (5/43, 11.6%, in both cases). Two cases were treated with methotrexate (2/43, 4.7%) and 2 isolated cases received apremilast and secukinumab. Withdrawal of immunotherapy due to psoriasis was not necessary in 15 patients (34.9%), whereas treatment was suspended temporarily in 6 patients (14%) and permanently in 5 (11.6%).

The response of the cancer to the anti-PD1 and anti-PDL1 is poorly described in these patients. The available data describe a good response in 12 patients and a lack of response in 3. Nevertheless, no correlation appears to exist between the antitumor response and the severity of the psoriasis, as occurs in vitiligo associated with the use of nivolumab for the treatment of melanoma.[8]

For the treatment of drug-induced psoriasis early recognition, and withdrawal, if possible, of the causal agent is generally recommended, together with the standard therapeutic regimen for psoriasis, in accordance with guidelines.[9] The use of cyclosporin is contra-indicated in psoriasis with an underlying cancer. The safety of TNF inhibitors and methotrexate is the subject of debate and little data is available on apremilast and other biological drugs.[10] Based on these data, we propose an algorithm for the treatment of patients with psoriasis due to anti-PD1 and anti-PDL1 (Fig. 2). The first point is the need for the oncologist to take a personal and family history of psoriasis from the patient. When psoriasis appears, the patient should be assessed rapidly by the dermatologist. The treatment considered must take into account the extension (PASI) and effect on quality of life (DLQI questionnaire) of the patient's psoria-

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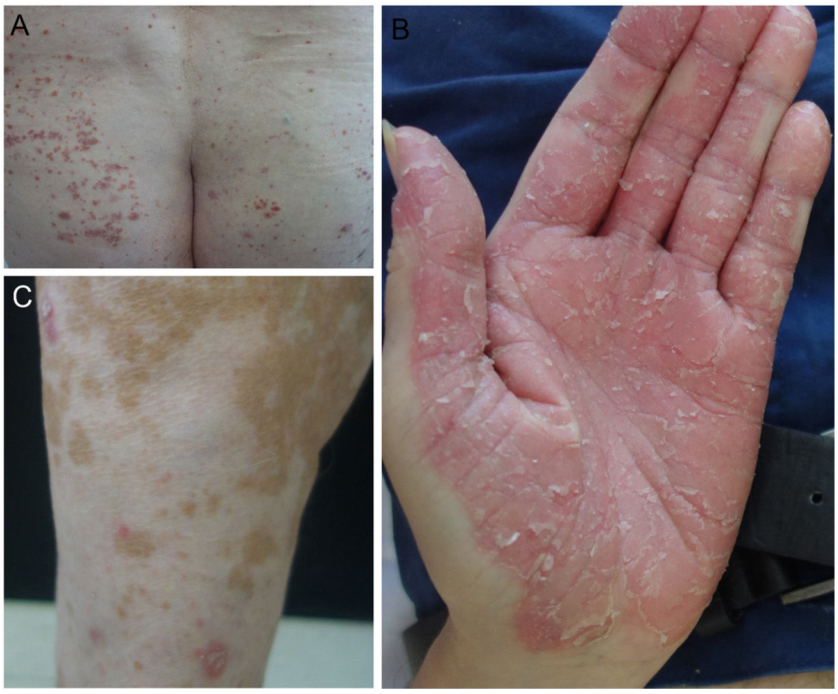

Figure 1 Patients in our department with psoriasis due to anti-PD1/anti-PDL1. (A) Guttate psoriasis. (B) Palmoplantar psoriasis. (C) Psoriasis plaques and vitiligo.

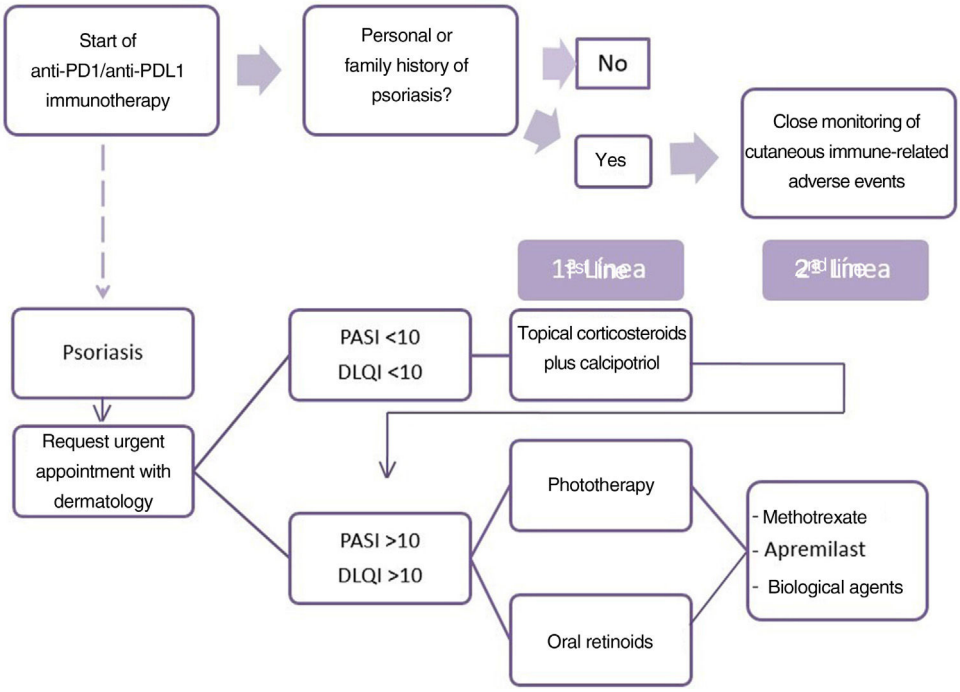

Figure 2 Proposed algorithm for managing psoriasis induced or exacerbated by anti-PD1/anti-PDL1.

sis. We therefore recommend prescribing topical treatment in mild psoriasis and prioritizing phototherapy and oral retinoids when systemic therapy is required, owing to the immunosuppressant effect of these drugs, due to the possible negative effect on the course of the cancer. In the event of a lack of response or contra-indication, apremilast, methotrexate, or biological treatments may be proposed after agreement with the oncologist.

Dermatologists must learn to recognize and treat the immune-associated cutaneous adverse effects due to anti-PD1 and anti -PDL1, which include psoriasis. Given its frequency, we highlight the need for periodic dermatologic follow-up of these patients. Cooperation with oncology is also essential to accelerate the diagnosis and provide the patients with the best therapeutic option to keep them free of

Table 1 Patients with psoriasis induced or exacerbated by anti-PD1/anti-PDL1 published in the literature as cases or series and their principal characteristics.

No.	Age, y/sex	Neoplasm	Anti-PD1/anti-PDL1, dosage regimen	Latency, wk	History of psoriasis	Treatment of psoriasis	Interruption of anti-PD1/anti-PDL1	Tumor response to anti-PD1/anti-PDL1	Lead author, year
1	80/M	Melanoma	Nivolumab, 2 mg/kg every 3 weeks	12	No	Systemic corticosteroids	No	Yes	Ohtsuka, 2015
2	65/M	Melanoma	Nivolumab, 2 mg/kg every 3 weeks	3	Yes	Topical corticosteroids plus calcipotriol and phototherapy, with no response. Oral retinoids with response	No	No Information	Kato, 2015
3	45/M	Renal cell carcinoma	Nivolumab, 2 mg/kg every 3 weeks	2	No	Topical corticosteroids plus calcipotriol	Yes, 21 d	Yes	Ruiz-Bañobre, 2017
4	87/M	Melanoma	Nivolumab, 2 mg/kg every 3 weeks	6	Yes	Systemic corticosteroids	Yes	No Information	Matsumura, 2015
5	80/F	Melanoma	Pembrolizumab, no information	3–6	No Information	Topical corticosteroids plus calcipotriol	Yes	Yes	Totonchy, 2016
6	67/M	Lung carcinoma	Pembrolizumab, no information	3	Yes	Oral retinoids	Yes, 4 wk	No Information	Sahuquillo-Torralba, 2016
7	NA	No Information	Pembrolizumab, no information	9	Yes	Topical corticosteroids plus calcipotriol and systemic corticosteroids	Yes, 1 wk	No Information	Sanlorenzo, 2015
8–24	Mean, 64.8 [35–87]/F (2), M (15)	Melanoma (9), lung carcinoma (8)	Pembrolizumab (5), nivolumab (11), atezolizumab (1), no information	No information	No Information	Topical corticosteroids (10), systemic corticosteroids (1), oral retinoids (5), and phototherapy (1)	No Information	No Information	Bonigen, 2017
25	67/M	Lung carcinoma	Nivolumab, 2 mg/kg every 3 weeks	3	No	Topical corticosteroids plus calcipotriol	No	No Information	Yamamoto, 2018
26	67/M	Melanoma	Pembrolizumab, 2 mg/kg every 3 weeks	15	Yes	Oral retinoids and phototherapy	Yes, 4 wk	Yes	Phadke, 2016
27–31	Mean, 66 [60–72]/F (1), M (4)	Lung carcinoma (3), urothelial carcinoma (1), tonsil cancer (1)	Pembrolizumab (1), nivolumab (2), durvalumab (2), no information	2–8	Yes (3), No (2)	Topical corticosteroids plus calcipotriol (1), phototherapy (3), methotrexate plus systemic corticosteroids (1)	Yes (1), No (4)	No Information	Voudouri, 2017

Table 1 (*Continued*)

No.	Age, y/sex	Neoplasm	Anti-PD1/anti-PDL1, dosage regimen	Latency, wk	History of psoriasis	Treatment of psoriasis	Interruption of anti-PD1/anti-PDL1	Tumor response to anti-PD1/anti-PDL1	Lead author, year
32	89/M	Melanoma	Nivolumab, 2 mg/kg every 3 weeks	2	No	Topical corticosteroids plus calcipotriol	No	No	Murata, 2017
33	80/M	Lung carcinoma	Nivolumab, 2 mg/kg every 3 weeks	16	No	Topical corticosteroids, systemic corticosteroids plus methotrexate	Yes, 4 wk	Yes	Law-Pingman, 2016
34	65/F	Melanoma	Nivolumab, 2 mg/kg every 3 weeks	20	Yes	Topical corticosteroids plus calcipotriol	Yes, spacing doses 3 weeks apart	Yes	De Bock, 2018
35	53/M	Diffuse large B-cell lymphoma	Nivolumab, 2 mg/kg every 3 weeks	12	No	Topical corticosteroids plus calcipotriol	Yes	No	Panayotis, 2018
36	74/F	Lung carcinoma	Nivolumab, 2 mg/kg every 3 weeks	12	Yes	Topical corticosteroids plus calcipotriol with no response Apremilast with response	No	Yes	Fattore, 2019
37	51/F	Lung carcinoma	Nivolumab, 2 mg/kg every 3 weeks	12	No	Topical corticosteroids plus calcipotriol	No	Yes	Guven, 2019
38	69/M	Lung carcinoma	Pembrolizumab, 200 mg every 3 weeks	12	Yes	Topical corticosteroids plus calcipotriol	No	No Information	Scanfi, 2019
39	63/F	Lung carcinoma	Pembrolizumab, 200 mg every 3 weeks	12	Yes	Topical corticosteroids plus calcipotriol with no response Secukinumab with response	No	Yes	Monsour, 2019
40	75/M	Urothelial carcinoma	Atezolizumab, 1200 mg every 3 weeks	3	Yes	Topical corticosteroids plus calcipotriol plus systemic corticosteroids.	Yes	No	Santos-Juanes, 2019
41	73/M	Urothelial carcinoma	Atezolizumab, 1200 mg every 3 weeks	16	No	Phototherapy	No	Yes	Our study
42	54/M	Laryngeal squamous cell carcinoma	Nivolumab, 2 mg/kg every 3 weeks	12	Yes	Oral retinoids	No	Yes	Our study
43	77/M	Melanoma	Nivolumab, 2 mg/kg every 3 weeks	20	No	Topical corticosteroids plus calcipotriol	No	Yes	Our study

Abbreviations: F indicates female; M, male.

lesions but without negatively affecting the neoplastic disease.

Conflict of interests

The authors declare that they have no conflict of interest.

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