



**Figure 3** A, Histology showing a dermal infiltrate of cords of cells from a lobular breast adenocarcinoma. Hematoxylin and eosin, original magnification  $\times 20$ . B, Immunohistochemistry showing groups of cells positive for GCDFP-15, indicating an origin in breast tissue. Original magnification  $\times 20$ .

It is currently thought that the increase in the incidence of metastases at these particular sites is due to the increased survival of cancer patients.<sup>9</sup> In conclusion, in our patient with a 15-year history of malignant disease,

the administration of multiple cycles of chemotherapy was interpreted as a factor that favored the appearance of this rare type of metastasis.

## References

1. Spencer PS, Helm TN. Skin metastases in cancer patients. *Cutis*. 1987;39:119–21.
2. Lookingbill DP, Spangler N, Helm KF. Cutaneous metastases in patients with metastatic carcinoma: A retrospective study of 4020 patients. *J Am Acad Dermatol*. 1993;29:228–36.
3. Brenner S, Tamir E, Maharshak N, Shapira J. Cutaneous manifestations of internal malignancies. *Clin Dermatol*. 2001;19:290–7.
4. Wong CY, Helm MA, Kaib RE, Zeitouni NC. The presentation, pathology, and current management strategies of cutaneous metastasis. *N Am J Med Sci*. 2013;5:499–504.
5. Mansour AM, Hidayat AA. Metastatic eyelid disease. *Ophthalmology*. 1987;94:667–70.
6. Esmaeli B, Cleary KL, Ho L, Safar S, Prieto VG. Leiomyosarcoma of the esophagus metastatic to the eyelid: A clinicopathologic report. *Ophtal Plast Reconstr Surg*. 2002;18:159–61.
7. Riley FC. Metastatic tumors of the eyelids: Clinicopathological study. *Surv Ophthalmol*. 1970;15:94–104.
8. Martorell-Calatayud A, Requena C, Díaz-Recuero JL, Haro R, Sarasa JL, Sanmartín O, et al. Mask-like metastasis: Report of 2 cases of 4 eyelid metastases and review of the literature. *Am J Dermatopathol*. 2010;32:9–14.
9. Schoenlaub P, Sarraux A, Grosshans E, Heid E, Cribier B. Survival after cutaneous metastasis: A study of 200 cases. *Ann Dermatol Venerol*. 2001;128:1310–5.

M.A. Díaz-Martínez,<sup>a,\*</sup> A. Almodóvar-Real,<sup>a</sup>  
R. Ruiz-Villaverde,<sup>b</sup> J.C. Ruiz-Carrascosa<sup>a</sup>

<sup>a</sup> *Servicio de Dermatología, Hospital Universitario San Cecilio, Granada, Spain*

<sup>b</sup> *Servicio de Dermatología, Hospital Universitario Virgen de las Nieves, Granada, Spain*

\* Corresponding author.

*E-mail address:* migueldimar88@gmail.com  
(M.A. Díaz-Martínez).

## Pembrolizumab: a New Drug That Can Induce Exacerbations of Psoriasis<sup>☆</sup>



### Pembrolizumab, un nuevo fármaco capaz de inducir un brote psoriasis

*To the Editor:*

Pembrolizumab is a monoclonal antibody that belongs to a group of new antitumor drugs that stimulate the immune

system. These drugs act by blocking key steps in the immune cascade. Specifically, pembrolizumab blocks the programmed cell death receptor (PD-1) whose function is to induce T-cell apoptosis, preventing excessive proliferation and function; this inhibition therefore leads to stimulation of the immune response.<sup>1</sup> A number of cancers, including melanoma and lung, kidney, and breast cancer, can present overexpression of PD-1 ligand (PD-L1) by the tumor cells as a mechanism of immune evasion. Blockade of the PD-1 receptor would help to end this evasion.<sup>2,3</sup>

We present the case of a 67-year-old man with a history of myocardial infarction and cerebellar stroke, diagnosed 3 months earlier with metastatic adenocarcinoma of the lung with PD-L1 expression in more than 5% of tumor cells, measured immunohistochemically. The patient was referred to

<sup>☆</sup> Please cite this article as: Sahuquillo-Torralba A, Ballester-Sánchez R, Pujol-Marco C, Botella-Estrada R. Pembrolizumab, un nuevo fármaco capaz de inducir un brote psoriasis. *Actas Dermosifiliogr*. 2016;107:264–266.



**Figure 1** Detail of the generalization of the psoriasis lesions after the second cycle of pembrolizumab.



**Figure 2** Clinical improvement after 3 months of treatment with acitretin, despite further infusions of pembrolizumab.

dermatology for evaluation and treatment of his psoriasis before entering a clinical trial investigating pembrolizumab for his lung neoplasm. The patient had psoriasis affecting the elbows, knees, and buttocks; the disease was stable on topical treatments, with a psoriasis area severity index (PASI) score of 3 and body surface area (BSA) involvement of 5%. The psoriasis deteriorated progressively after the first cycle of pembrolizumab, with a PASI score of 22 and BSA of 60%; after the second infusion, the severity became almost compatible with erythrodermic psoriasis, with a BSA of 81% and a PASI score of 33 (Fig. 1). Treatment was

started with acitretin at a dose of 25 mg/d. This had to be increased to 35 mg/d after the deterioration seen during the second cycle. The tumor response to pembrolizumab was excellent after the second infusion of the drug, as was the improvement of his psoriasis with acitretin after 6 weeks of treatment. It was therefore decided to continue treatment with both drugs. There have been no further outbreaks of psoriasis during the following 3 infusion cycles. Three months after the initial outbreak, the patient had a PASI score of 4 (Fig. 2), which allowed us to reduce the dose of acitretin to 20 mg/d.

Psoriasis is a chronic inflammatory disease. Evidence points ever more to an autoinflammatory disorder in which hyperreactive T cells produce large amounts of interleukins and tumor necrosis factor, leading to increased epidermal turnover. To date there are no reports of a deterioration or induction of psoriasis in patients treated with pembrolizumab or other immune checkpoint blockers, though, given the drug's mechanism of action and the pathophysiology of psoriasis, it would appear logical that such adverse reactions could occur. Recent studies have shown decreased expression of the PD-1 receptor in peripheral blood lymphocytes in patients with psoriatic arthritis and rheumatoid arthritis; this appears to show an inverse correlation with severity of the joint disease, as it would reduce the lymphocyte population susceptible to inhibition by the PD-1 pathway, although it does not seem to affect the PASI of patients with psoriasis.<sup>4,5</sup> Based on this evidence, it may be surmised that certain quantitative changes take place in the PD-1<sup>+</sup> T cells in patients with psoriasis, leading to T-cell hyperactivity that would increase exponentially with the use of PD-1-receptor blockers, explaining the notable deterioration in our patient's psoriasis. Confirmation of this hypothesis would require larger series of patients with psoriasis, and would need to include measurement of PD-1<sup>+</sup> lymphocyte count by flow cytometry and immunohistochemistry techniques and of the PD-L1 levels by immunohistochemistry. In the way, we could define more accurately the pathophysiology of psoriasis and even open the door to new therapeutic targets.

There are still no publications on the treatment of psoriasis induced or exacerbated by immune checkpoint blockers. Based on our experience, acitretin could be a good option to achieve optimal control of a patient's psoriasis and would be compatible with continuation of the anticancer treatment. Studies of patient series are needed to confirm our clinical experience.

In general, the main side effects associated with the new immune checkpoint blockers are derived from their pharmaceutical action, provoking an autoimmune response against different body tissues. The most commonly described alterations have been hypo- and hyperthyroidism, hepatitis, diarrhea, enterocolitis, and hypophysitis. Skin manifestations include pruritus and a maculopapular rash, and there have even been reports of erythroderma, Stevens-Johnson syndrome, and toxic epidermal necrolysis. Patients at highest risk of developing these side effects are those with a history of autoimmune disease, which is a relative contraindication to the use of such drugs.<sup>6-8</sup>

The immune checkpoint blockers are achieving a good response in certain types of cancer.<sup>9</sup> This would suggest that

their use will increase in cancer patients. We must be alert to their adverse effects and perform more thorough follow-up and therapeutic management in patients with underlying autoimmune or autoinflammatory diseases.

## Acknowledgments

We would like to thank Dr. Óscar Juan Vidal of the Oncology Department of Hospital Universitari i Politècnic La Fe in Valencia, Spain, for his help.

## References

1. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer*. 2012;12:252–64.
2. Drake CG, Lipson EJ, Brahmer JR. Breathing new life into immunotherapy: Review of melanoma, lung and kidney cancer. *Nat Rev Clin Oncol*. 2014;11:24–37.
3. Ribas A. Tumor immunotherapy directed at PD-1. *N Engl J Med*. 2012;366:2517–9.
4. Peled M, Strazza M, Azoulay-Alfaguter I, Mor A. Analysis of programmed death-1 in patients with psoriatic arthritis. *Inflammation*. 2015;38:1580.
5. Li S, Liao W, Chen M, Shan S, Song Y, Zhang S, et al. Expression of programmed death-1 (PD-1) on CD4<sup>+</sup> and CD8<sup>+</sup> T cells in rheumatoid arthritis. *Inflammation*. 2014;3:116–21.
6. Weber JS, Kahler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. *J Clin Oncol*. 2012;30:2691–7.
7. Tarhini A. Immune-mediated adverse events associated with ipilimumab CTLA-4 blockade therapy: The underlying mechanisms and clinical management. *Scientifica (Cairo)*. 2013;2013:857519.
8. Tepy BA, Lipson EJ. Identification and management of toxicities from immune checkpoint-blocking drugs. *Oncology (Williston Park)*. 2014;28 Suppl 3:S30–8.
9. Brahmer JR, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med*. 2012;366:2455–65.

A. Sahuquillo-Torrallba,\* R. Ballester-Sánchez,  
C. Pujol-Marco, R. Botella-Estrada

*Servicio de Dermatología, Hospital Universitari i Politècnic La Fe, Universidad de Valencia, Valencia, Spain*

\* Corresponding author.

E-mail address: saucodos@gmail.com

(A. Sahuquillo-Torrallba).