# IMMUNE CHECKPOINT INHIBITORS – INDUCED VITILIGO

ALEXANDRU OANȚĂ*, TRAIAN CONSTANTIN**, IOANA VLAS*, SMARANDA ȚĂREAN*

**Summary**

***Introduction***: *Immune checkpoint inhibitors (anti-CTLA-4, anti-PD-1, anti-PD-L1 monoclonal antibodies) represent a new class of medication in cancer therapy. The toxicity of immune checkpoint inhibitors is primarily immunologically mediated by the reactivation and proliferation of induced T lymphocytes. However, the incidence of these reactions varies depending on the monoclonal antibody used, being similar for each molecule. These side effects can theoretically affect all organs as a whole.*

***Clinical case:*** *We present the case of 62 year old patient with metastatic melanoma with left axillary and inferior paratracheal lymphadenopathy which are metabolically active. The patient was treated with intravenous pembrolizumab. The treatment was not followed by the appearance of toxicity except for the appearance of vitiligo on the scalp.*

***Discussion:*** *Dermatological toxicity occurs with both anti-PD-1 (nivolumab, pembrolizumab) and anti-CTLA-4 (ipilimumab) treatments regardless of the type of tumor treated [1-6]. The most common skin conditions are rash, maculopapular rash, pruritus and vitiligo.*

***Keywords***: *vitiligo, immune checkpoint inhibitors, melanoma, monoclonal antibody.*

*Received: 30.07.2021* *Accepted: 2.09.2021*

## Introduction

Immune checkpoint inhibitors (anti-CTLA-4, anti-PD-1, anti-PD-L1 monoclonal antibodies) represent a new class of medication in cancer therapy. The toxicity of immune checkpoints inhibitors is mainly immunologically mediated by the reactivation and proliferation of induced T lymphocytes. However, the incidence of these reactions varies depending on the monoclonal antibody used, being similar for each molecule. These side effects can theoretically affect all organs causing of thyroiditis, dermatitis, pneumonia, colitis, hepatitis, hypophysitis, uveitis, polyneuritis, pancreatitis.

Dermatological toxicity occurs with both anti-PD-1 (nivolumab, pembrolizumab) and anti-CTLA-4 (ipilimumab) regardless of the type of tumor treated, affecting more than one-third of patients treated with this medication [1-6]. The most common skin conditions are rash, maculopapular rash, pruritus and vitiligo.

## Clinical case

A 62-year-old patient is consulted for achromic plaques located on the scalp, visible with the Wood's lamp evoking the diagnosis of vitiligo.

The patient underwent surgery in 2012 for melanoma located on the posterior thorax with the Breslow index of 2 mm and the Clark level V. In October 2018 the patient presented a subcutaneous nodular tumor located on the posterior thorax that was removed, proving to be a metastasis of melanoma. In December 2018, at the PET-CT examination, hyperfixed lung nodules were highlighted in the area of the left lower lobe, requiring a left thoracotomy with a

* S.C. Dermamed SRL, Brașov.
** Clinical Hospital "Prof. Dr. Th. Burghele" Bucharest.

left lower lobectomy. In June 2020, a new PET-CT examination revealed recent left axillary and lower paratracheal adenopathy metabolically active. Intravenous pembrolizumab treatment was introduced. The treatment was not followed by any toxicity except for the appearance of vitiligo lesions on the hairy scalp 6 weeks after its introduction with subsequent extension (Fig. 1, Fig. 2).

## Discussions

Vitiligo may occur in patients treated with anti-PD-1 for metastatic melanoma [7]. The overall incidence of vitiligo in metastatic melanoma treated with immune checkpoint inhibitors was estimated at 8.3% and 7.5% in patients treated with pembrolizumab and nivolumab [8.9], respectively, with higher incidences of around 25% [10,11]. In contrast, the incidence of vitiligo is much lower for ipilimumab. However, the occurrence of vitiligo is exceptional in patients treated with immune checkpoint inhibitors for another cancer such as myeloid leukemia [12] or hepatocellular carcinoma [13], and the possibility of underestimating the diagnosis of vitiligo in the detection of these patients in medical oncology.

The appearance of vitiligo during treatment is significantly associated with improved survival, representing an indirect marker of the antitumor efficiency of anti-PD-1 treatment [14]. Vitiligo lesions potentially correspond to a cross-lymphocyte reaction between tumor antigens and certain melanocyte epitopes (MART-1, GP100, TRP1-2 or tyrosinase). [6,10,11]

Vitiligo occurs after several months of treatment with immune checkpoint inhibitors with a progressive spread and may be preceded by an inflammatory phase. The distribution of lesions can be bilateral and symmetrical, [10,16] diffuse [6,10] but also focal or segmental. [11,17] Larsabal [17] suggested that immunotherapy-induced vitiligo different from the classical one

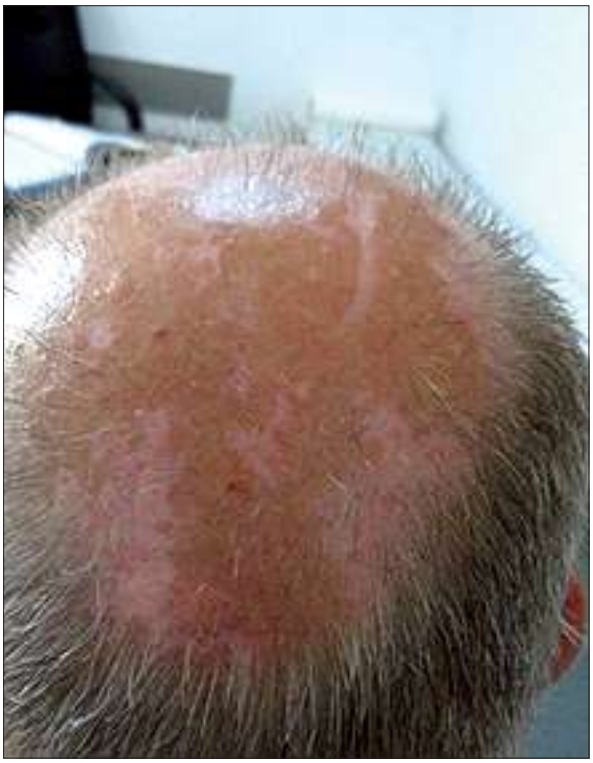

*Figure 1*

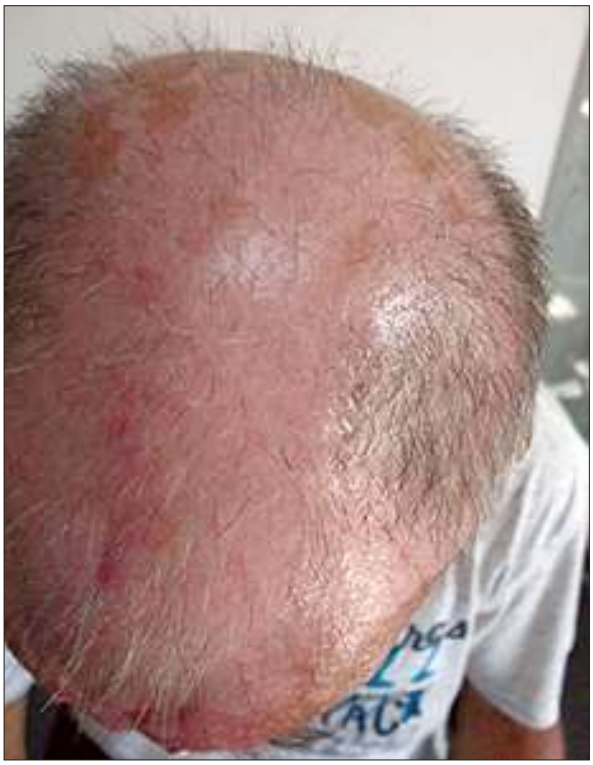

*Figure 2*

*Figure 1 and Figure 2 – Clinical aspect of vitiligo appeared after the introduction of pembrolizumab treatment.*

by predominating on the photoexposed areas, being rarely associated with the Kobner phenomenon and respecting the classic "bastion" areas and affecting the hair follicle more frequently. The author also suggests a different pathophysiological mechanism in the occurrence of vitiligo induced by immunotherapy.

During treatment with immune checkpoints inhibitors, depigmentation may also occur around skin metastases, nevi (Sutton phenomenon) or scars after lymph node removal. [10,17]

Isolated depigmentation of the eyelashes, eyebrows or hair appered, sometimes acompanied by plaque vitiligo. [18] Vitiligo usually persists for a long time after stopping immunotherapy [6] and may affect patients quality of life.

## Bibliography


1. Postow MA, Callahan MK, Wolchok JD. Immune checkpoint blockade in cancer therapy. *J Clin Oncol* 2015; 33: 1974-82.
2. Naidoo J, Page DB, Li BT, Connell LC, Schindler K, Lacouture ME, et al. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. *Ann Oncol* 2015; 26: 2375-91.
3. Weber JS, Hodi FS, Wolchok JD, Topalian SL, Schadendorf D, Larkin J, et al. Safety profile of nivolumab monotherapy: a pooled analysis with advanced melanoma. J *clin Oncol* 2017; 35: 785-92.
4. Weber JD, Kahler KC, Hauschild A. Management of immune related adverse events and kinetics of response with ipilimumab. *J Clin Oncol* 2012; 30: 2691-7.
5. Hassel JC, Heinzerling L, Aberle J, Bahr O, Elgentler TK, Grimm MO, et al. Combined immune checkpoint blockade (anti-PD-1/anti-CTLA-4: evaluation and management of adverse drug reactions. *Cancer Treat Rev* 2017; 57: 36-49.
6. Freeman-Keller M, Kim Y, Cronin H, Richards A, Gibney G, Weber JS, et al. Nicolumab in resected and unresectable metastatic melanoma: characteristics of immume-related adverse events and association with outcomes. *Clin Cancer Res* 2016; 22: 886-94.
7. Teulings H-E, Limpens J, Jansen SN, Zwinderman AH, Reitsma JB, Spuls PI, et al. Vitiligo-like depigmentation in patients with stage III-IV melanoma receiving immunotherapy and its association with survival: a systematic review and meta-analysis. *J Clin Oncol* 2015; 33: 773-81.
8. Belum VR, Benhuri B, Postow MA, Hellmann MD, Lesokhin AM, Segal NH, et al, Characterisation and management of dermatologic adverse events to agents targeting the PD-1 receptor. *Eur J Cancer* 2016; 60: 12-25.
9. Dai J, Belum VR, Wu S, Sibaud V, Lacouture ME. Pigmentary changes in patients treated with targeted anticancer agents: a systematic review and multi-institutional retrospective study. *J Dermatol* 2017; 44: 117-22.
10. Hua C, Boussemart L, Mateus C, Routier E, Boutros C, Cazenave H, ET AL. Association of vitiligo with tumor response in patients with metastatic melanoma treated with pembrolizumab. *JAMA Dermatol* 2016; 152: 45-51.
11. Nakamura Y, Tanaka R, Asami Y, Teramoto Y, Imamura T, Sato S, et al. Correlation between vitiligo occurrence and clinical benefit in advanced melanoma patients treated with nivolumab: a multi-institutional retrospective study. *J Dermatol* 2017; 44: 117-22.
12. Yin ES, Totonchy MB, Leventhal JS. Nivolumab-associated vitiligo-like depigmentation in a patient with acute myeloid leukemia: A novel finding. *JAAD Case Rep* 2017; 3: 90-2.
13. Rodriguez-Lomba E, Molina-Lopez I, Suarez-Fernandez R, Baniandres-Rodriguez O. Vitiligo-like lesions and immune checkpoint inhibition therapy: is it truly an adverse event exclusive to patients with melanoma? *Clin Exp Dermatol* 2018: 10, http://dx.doi.org/10.1111/ced.13382.
14. V. Sibaud, S. Boulinguez, C. Pages, L. Riffaud, L. Lamant, C. Chira, S. Boyrie, E. Vigarios, E. Tournier, N. Meyer. Toxicites dermatologiques des inhibiteurs de checkpoint immunologiques. *Ann Dermatol Venereol* 2018; 145: 313-330.
15. Hwang SJ, Carlos G, Wakade D, Byth K, Kong NY, Chou S, et al. Cutaneous adverse events (AEs) of anti-programmed cell death (PD)-1 therapy in patients with metastatic melanoma; a single-institution cohort. *J Am Acad Dermatol* 2016; 74: 455-61.
16. Minkis K, Gardem BC, Wu S, Pulitzer MP, Lacouture ME. The risk of rash associated with ipilimumab in patients with cancer: a systematic review of the literature and meta-analysis. *J Am Acad Dermatol* 2013; 69: e121-8.

17. Larsabal M, Marti A, Jacquemin C, Rambert J, Thiolat D, Dousset L, et al. Vitiligo-like lesions occurring in patients receiving anti-programmed cell death-1 therapies are clinically and biologically distinct from vitiligo. *J Am Acad Dermatol* 2017; 76: 863-70.
18. Hofmann L, Forschner A, Loquai C, Goldinger SM, Zimmer L, Ugurel S, et al. Cutaneous, gastrointestinal, hepatic, endocrine, and renal side effects of anti-PD-1 therapy. *Eur J Cancer* 2016 ;60: 190-209.

Conflict of interest
NONE DECLARED

*Correspondance address:* Dr. Ioana-Maria Vlas
Dermamed SRL, Brașov
Sebeș Municipal Hospital
New Life Med Clinic, Alba-Iulia
Medivers Cllinic , Brașov
E-mail: vlas.ioana@gmail.com