Extensive "halo naevi" phenomenon and regression of melanin during nivolumab treatment in metastatic melanoma: A predictor of a better outcome?

Dear Editor,

Hypopigmentation phenomena like vitiligo and halo nevus development in melanoma patients treated with immune checkpoint inhibitors (ICI) are well described yet poorly understood. Vitiligo-like depigmentation in stage III-IV melanoma patients, treated with ICI, was found to be associated with prolonged progression-free survival, improved overall survival, and decreased risk of disease progression, compared to patients without vitiligo, pointing to depigmentation phenomena as a proxy of response to immunotherapy.[1] On the other hand, halo nevus, or Sutton phenomenon, which is defined as a central pigmented nevus surrounded by a sharp zone of hypopigmentation, is a rarer clinical manifestation seen in ICI-treated patients and his prognostic value, as well as any differences from the classical form, remains undefined. Moreover, in clinical practice, few pigmented naevi are generally involved in Sutton's phenomenon, and not many descriptions have been reported on extensive halo nevus development (defined as involvement on more than 50% of pre-existing naevi) during ICI treatment. Finally, recent evidence suggests that multiple gray dots at the dermoscopic observation of the naevi (Figure 1A.), an indicator of immune-mediated regression, could be associated with a better outcome. If this was confirmed, dermoscopy could represent a tool for early detection of a response to immunotherapy.[2]

Herein, we report the case of a 63-year-old man diagnosed with lower leg superficial spreading melanoma (pT3b), Breslow 3 mm, ulcerated, 10% regression, BRAF V600E mutated, treated by excision in 2019. Subsequently, he underwent sentinel lymph node biopsy (SLNB), which was negative for lymph node involvement. The concomitant staging CT scan showed a right adrenal metastasis (Stage IVc). According to the patient's preference of a monthly intravenous infusion instead of a daily oral regimen with BRAF-MEK inhibitors, treatment with anti-PD1 nivolumab was started (480 mg every 4 weeks). At the 12-week visit, an achromic halo appeared on the left arm around a pre-existing nevus (Figure 1B). The halo phenomenon progressively involved more than 50% of naevi on the body during the following months. In few cases, the sudden disappearance of pre-existing naevi was observed, resulting in achromic macules only (Figure 1C). In addition, the dermoscopic evaluation revealed complete regression of the melanin in some other naevi (Figure 1D). Subsequent imaging assessments showed stable disease with no signs of disease progression. To date, the patient has received 30 infusions of nivolumab for a total time of 120 weeks and remains progression-free, showing a good response to the immunotherapy.

A peripheral achromic halo surrounding primary melanomas or cutaneous metastases has been described and interpreted as manifestations of cytotoxic response to tumoral cells.[1] Moreover, concomitant regression of multiple naevi without any visible halo phenomenon and maintained complete remission of metastatic melanoma has been described during ICI treatment.[1] It has been

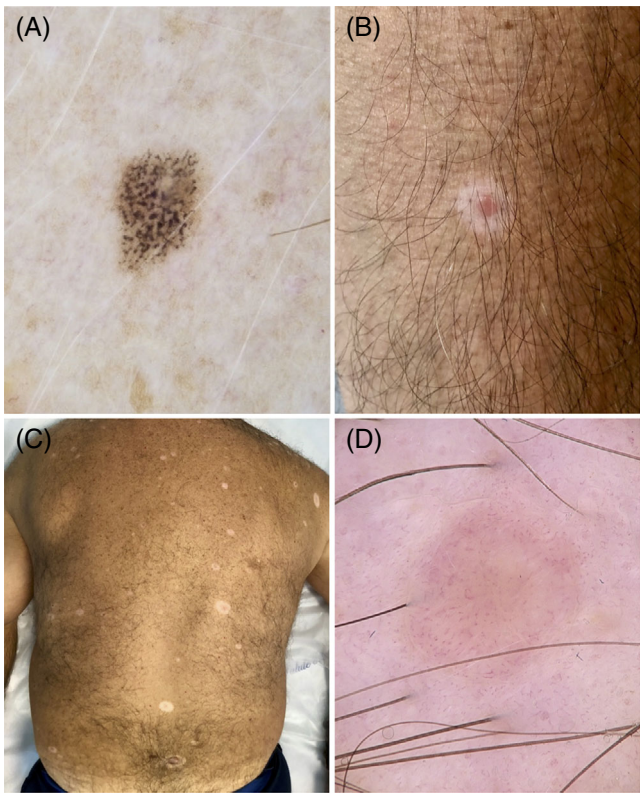

FIGURE 1 (A) Multiple gray dots, indicative of an ongoing immune process of regression, in a patient's nevus treated with nivolumab. (B) Achromic halo involving a pre-existing nevus on the right arm after 12 weeks of nivolumab treatment in a metastatic melanoma patient. (C) Extensive Sutton's phenomenon involving multiple naevi on the back, including intradermal naevi. In some cases, the disappearance of the pre-existing nevus left an achromic macule only. (D) Dermoscopic features of a halo nevus on the right arm showing complete regression of melanin.

Francesco Cavallo and Gabriele Roccuzzo contributed to this paper.

hypothesized that these occurrences result from immune responses against shared melanocytic antigens between malignant and benign melanocytic lesions (i.e., MART-1, gp100, and tyrosinase-related proteins 1 and 2).[3] However, a deep understanding of the relationship between melanoma and regressive phenomena both at the level of the primary lesion and at a distance is still missing.

As for approved anti-PD1 drugs in advanced melanoma, extensive halo phenomenon, defined as involvement of at least 50% of the cutaneous naevi in a patient, has been reported only by Nicolétis-Lombart et al. during pembrolizumab treatment and by Plaquevent et al during ipilimumab treatment. In both cases, complete remission of metastatic melanoma was obtained within 24 and 6 months, respectively.[3,4]

To the best of our knowledge, we present the first case of extensive Sutton phenomenon during treatment with nivolumab for metastatic melanoma. Notably, this process was associated in our patient with complete regression of the melanin in some naevi. While the fading of naevi during targeted therapy for metastatic melanoma is a commonly reported and dermoscopically characterized entity,[2] there is still much to explore about immune-mediated regression of moles during immunotherapy treatment. This case report supports the hypothesis that the extended Sutton phenomenon and the regression of the melanin may be associated with a better prognosis as it has been previously observed for vitiligo-like depigmentation. Moreover, it should be noted that, although the natural history of halo naevi is that a subgroup of them undergo involution, this process usually takes more than 8 years to unfold,[5] while in our patient occurred in less than 2 years. This fact, combined to the eruptive and diffuse nature of the phenomenon, indicates that the development of ICI-induced halo naevi is a different clinical entity than the classical form, as it has been previously demonstrated for ICI-induced vitiligo-like depigmentation.[6] However, larger studies are needed to fully assess the supposed prognostic value in metastatic melanoma patients and the distinct clinical characteristics of this occurrence.

AUTHOR CONTRIBUTIONS

All authors have contributed significantly to this publication.

ACKNOWLEDGMENT

The patient in this manuscript has given written informed consent to publication of his case details.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Francesco Cavallo[1]
Gabriele Roccuzzo[1]
Gianluca Avallone[1]
Claudio Conforti[2]
Iris Zalaudek[2]
Silvia Giordano[1]
Marco Rubatto[1]
Paolo Fava[1]
Simone Ribero[1]
Pietro Quaglino[1]

[1]*Section of Dermatology, Department of Medical Sciences, University of Turin, Turin, Italy*
[2]*Dermatology Clinic, Maggiore Hospital, University of Trieste*

Correspondence
Francesco Cavallo, Section of Dermatology, Department of Medical Sciences, University of Turin, Via Cherasco 23, 10126, Turin, Italy.
Email: fcavallo93@gmail.com

Francesco Cavallo and Gabriele Roccuzzo contributed to this paper.

ORCID

Francesco Cavallo https://orcid.org/0000-0001-9296-826X
Gianluca Avallone https://orcid.org/0000-0001-7253-2370
Claudio Conforti https://orcid.org/0000-0001-5126-8873
Marco Rubatto https://orcid.org/0000-0003-1706-656X
Simone Ribero https://orcid.org/0000-0002-0098-1406

REFERENCES

1. Quach HT, Johnson DB, LeBoeuf NR, Zwerner JP, Dewan AK. Cutaneous adverse events caused by immune checkpoint inhibitors. *J Am Acad Dermatol*. 2021;85(4):956-966.
2. Farinazzo E, Zelin E, Agozzino M, et al. Regression of nevi, vitiligo-like depigmentation and halo phenomenon may indicate response to immunotherapy and targeted therapy in melanoma. *Melanoma Res*. 2021;31(6):582-585.
3. Plaquevent M, Greliak A, Pinard C, Duval-Modeste AB, Joly P. Simultaneous long-lasting regression of multiple nevi and melanoma metastases after ipilimumab therapy. *Melanoma Res*. 2019;29(3):311-312.
4. Nicolétis-Lombart I, Kervarrec T, Zaragoza J, Machet MC, Samimi M. Multiple "halo nevi" occurring during pembrolizumab treatment for metastatic melanoma. *Int J Dermatol*. 2019;58(6):739-741.
5. Aouthmany M, Weinstein M, Zirwas MJ, Brodell RT. The natural history of halo nevi: a retrospective case series. *J Am Acad Dermatol*. 2012;67(4):582-586.
6. Ramondetta A, Ribero S, Conti L, et al. Clinical and pathological relevance of drug-induced vitiligo in patients treated for metastatic melanoma with anti-PD1 or BRAF/MEK inhibitors. *Acta Derm Venereol*. 2020;100(1):adv00001.