Dermatology Practical & Conceptual

Regression of Multiple Melanocytic Nevi in Two Patients on Nivolumab for Metastatic Melanoma

Gloria Baeza-Hernández[1], Ricardo Francisco Rubio-Aguilera[1], Anastasia Alejandra Garrido-Ríos[1], Helena Álvarez-Garrido[1], Cristina Martínez-Morán[1], Jesús Borbujo[1]

1 Department of Dermatology. Hospital Universitario de Fuenlabrada, Madrid, Spain

Key words: nivolumab, regression, melanocytic nevi, melanoma, dermoscopy

Citation: Baeza- Hernández G, Rubio-Aguilera RF, Garrido-Ríos AA, Álvarez-Garrido H, Martínez-Morán C, Borbujo J. Regression Of Multiple Melanocytic Nevi In Two Patients On Nivolumab For Metastatic Melanoma. *Dermatol Pract Concept.* 2023;13(1):e2023022. DOI: https://doi.org/10.5826/dpc.1301a22

Accepted: May 26, 2022; **Published:** January 2023

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

Corresponding Author: Gloria Baeza-Hernández, Servicio de Dermatología, Hospital de Fuenlabrada, Camino del Molino 2, 28942 Fuenlabrada, Madrid. E-mail: gloria.baeza@salud.madrid.org

Introduction

Immunotherapy (anti-PD1 and anti-CTLA4) has been described to achieve complete regression of non-metastatic melanoma, assessed by reflectance confocal microscopy; however, their effects on benign melanocytic lesions have not been thoroughly studied and may be underreported [1]. Herein we report 2 patients with regression of multiple nevi while on treatment with nivolumab for metastatic melanoma.

Case Presentation

Two patients, suffering from metastatic melanoma treated with nivolumab (Table 1), attended our outpatient clinic for their annual digital dermoscopic monitoring. They were not aware of any changes or new melanocytic lesions. On physical examination, no new lesions were detected since their last visit one year before; with dermoscopy several of their benign melanocytic nevi had lightened and no atypical or malignant lesions were observed (Figures 1 and 2). Both patients had experienced disease progression despite anti-PD1 treatment.

Conclusions

Benign melanocytic nevi regression is an emerging secondary effect of anti-PD1 drugs nivolumab and pembrolizumab. Although these drugs are used on other cancer treatments, this secondary effect seems to be more frequent in patients undergoing treatment for melanoma [2]. In an observational study published in 2017, 11 patients treated

Table 1. Patient characteristics.

Metastatic melanoma	Patient 1	Patient 2
Sex	Male	Male
Age, years	50	60
Location	Abdomen	Back
Mutation	BRAF V600E/E2/D	
Treatment before/after nivolumab	Before: dabrafenib-trametinib, which was stopped because metastases spread to his lungs and inguinal and retroperitoneal lymph nodes (lymphadenectomy was performed)	No
Nivolumab start and end dates/doses mg/weeks	2021 – ongoing/ 240 mg every 2 weeks	2020-2021/ 480 mg every 4 weeks
Lightening of nevi observed with digital dermoscopy	2021: > 80% of his nevi. (Previous digital monitoring: 2020)	2022: > 60% of his nevi. (Previous digital monitoring: 2021)
Nivolumab secondary effects	Yes, vitiligo-like lesions	Yes, nivolumab-induced thyrotoxicosis and subsequent hypothyroidism
Disease progression while on nivolumab	Yes, new lymph node metastases near his melanoma scar on the abdomen and small bowel metastases (2022)	Yes, dermal melanoma metastases on the back (2021)
Second melanoma while on treatment	Yes, melanoma in situ on his back while on dabrafenib-trametinib (2020).	Yes, melanoma on his right leg (Breslow thickness 3.4 mm) while on nivolumab (2021).
	Both were detected in the annual digital dermoscopy monitoring visit.	
Other	-	A lung adenocarcinoma was diagnosed while on nivolumab (2021) and later excised. He has developed mediastinal lymph node metastases, awaiting treatment.

with anti-PD1 for metastatic melanoma (10 with pembrolizumab and 1 with nivolumab) had more lightened nevi than controls during follow-up (49% versus 19%); nevertheless, differences were not statistically significant [3]. Lightening without halo is a known phenomenon, especially in patients treated with pembrolizumab [4,5]. There are few reports regarding regression of melanocytic nevi in patients treated with nivolumab: one similar to our patient, with no inflammation or halo, and another patient who experimented inflammation before regression, with no halo [6,7]. Though some articles suggest that regression of melanocytic nevi may be related to the therapeutic effect of the anti-PD1 drug and could be interpreted as a sign of good therapeutical response, our patients both experimented progression despite nivolumab treatment; therefore, more studies are required to shed light on this matter [2,5,7]. One of our patients also had vitiligo-like phenomenon, which has been suggested to be associated with a better prognosis [2].

Furthermore, some other questions remain still unanswered: it could be asked why some patients experience only lightening without halo, while others have vitiligo-like reactions and halo nevi, and whether the underlying mechanism is the same [3]; why some patients have clinical inflammation but most of them do not according to the literature. Lastly, it is debatable whether regression of nevi with anti-PD1 is as rare as it seems today, for it may be an unnoticed secondary effect in other cancer patients (lung,

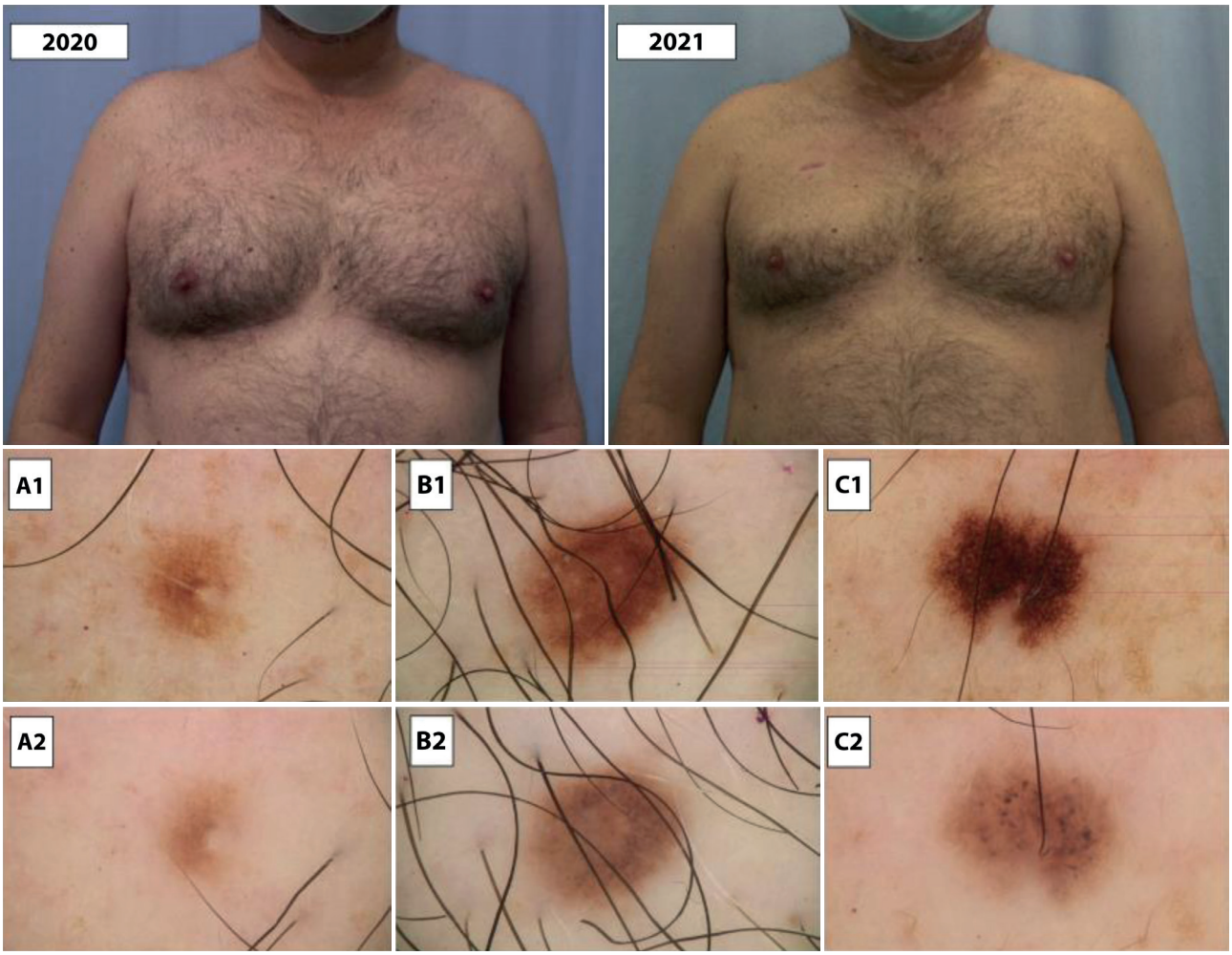

Figure 1. Clinical images of patient 1: 2020 (left) and 2021 (right). Three examples of lesions registered in digital monitoring of patient 1. (A1-C1) First row shows these benign melanocytic in 2020. (A2-C2) Second row shows the same lesions one year later in 2021, 6 months after starting treatment with nivolumab.

kidney, head, and neck, etc.) who are not followed up in a dermatology clinic.

One may well wonder about the utility of digital monitoring of patients with metastatic melanoma undergoing treatment with immune checkpoint inhibitors (ICI). In a recent single-center retrospective cohort study 42 patients (1.9%) with metastatic melanoma who received treatment with ICI developed new melanomas; thus, prospective studies with longer follow-up are needed to draw a solid conclusion [8]. While on ICI, both of our patients had a second melanoma that was detected in the digital follow-up; we want to highlight that in case 1, with longer digital monitoring, melanoma was detected in situ, in line with the findings of Lallas et al where almost 70% of second primary melanomas detected during surveillance were in situ [9]. We think that, when available and feasible, monitoring with digital dermoscopy and total body photography should be offered to all melanoma patients, as it helps in the early diagnosis of melanoma, with some lesions being only diagnosed by dermoscopic changes in the absence of melanoma-specific criteria [9].

Regression of multiple nevi is a scarcely reported secondary effect of nivolumab we should be aware of, especially in dermoscopic monitoring. It may be an overlooked effect because patients treated with anti-PD1 for cancers other than melanoma are not usually examined by a dermatologist. Its prognostic meaning is still unclear.

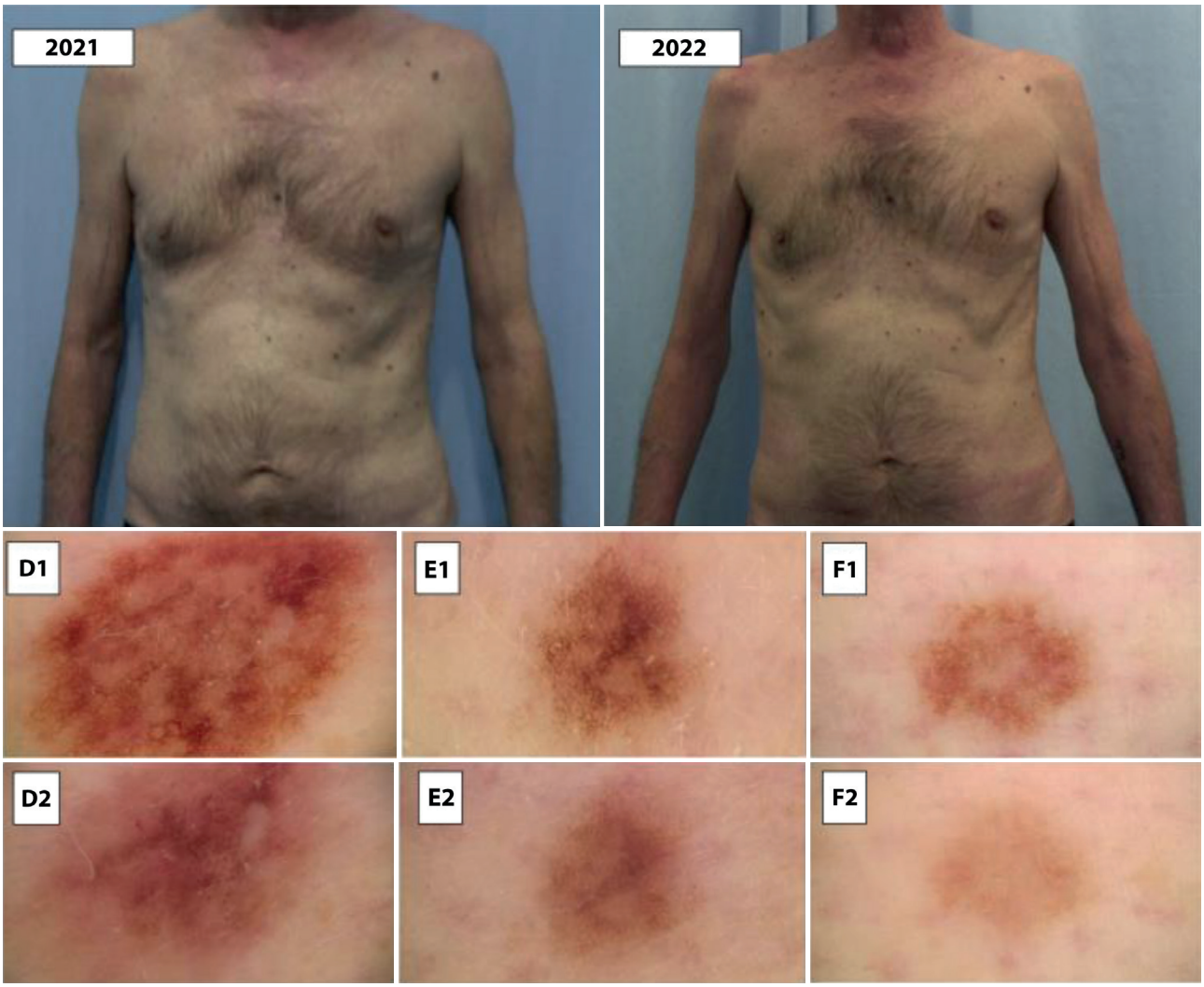

Figure 2. Clinical images of patient 2: 2021 (left) and 2022 (right). Three lesions registered in digital monitoring of patient 2. (D1-F1) First row shows these benign melanocytic nevi in 2021, while on nivolumab treatment. (D2-F2) Second row displays the same lesions one year later in 2022, 6 months after finishing treatment with nivolumab.

References

1. Navarrete-Dechent C, Cordova M, Postow MA, et al. Evaluation of the Response of Unresectable Primary Cutaneous Melanoma to Immunotherapy Visualized With Reflectance Confocal Microscopy. *JAMA Dermatology*. 2019;155(3):347. DOI:10.1001/jamadermatol.2018.3688. PMID: 30624578. PMCID: PMC6440283.
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. DOI:10.1097/CMR.0000000000000776. PMID: 34433200.
3. Zhao CY, Hwang SJE, Wakade D, Carlos G, Anforth R, Fernández-Peñas P. Melanocytic lesion evolution patterns with targeted therapies and immunotherapies for advanced metastatic melanoma: An observational study. *Australas J Dermatol*. 2017;58(4):292-298. DOI:10.1111/ajd.12645. PMID: 28707403.
4. Wolner ZJ, Marghoob AA, Pulitzer MP, Postow MA, Marchetti MA. A case report of disappearing pigmented skin lesions associated with pembrolizumab treatment for metastatic melanoma. *Br J Dermatol*. 2018;178(1):265-269. DOI:10.1111/bjd.15354. PMID: 28132411. PMCID: PMC5533648.
5. Mauzo SH, Tetzlaff MT, Nelson K, et al. Regressed melanocytic nevi secondary to pembrolizumab therapy: an emerging melanocytic dermatologic effect from immune checkpoint antibody blockade. *Int J Dermatol*. 2019;58(9):1045-1052. DOI:10.1111/ijd.13833. PMID: 29152725.
6. Vazquez B, Velasco R, Martin JM, Gonzalez I, Ramon MD. Regression of multiple melanocytic nevi associated with nivolumab treatment for metastatic melanoma. *Int J Dermatol*. 2019;58(11):1331-1333. DOI:10.1111/ijd.14340. PMID: 30536371.
7. Nakamura Y, Fujino T, Kagamu H, et al. Induction of immune reaction in benign melanocytic nevi without halo during nivolumab therapy in a patient with melanoma. *JAMA Dermatology*. 2017;153(8):832-834. DOI:10.1001/jamadermatol.2017.0615. PMID: 28492864.

8. Nanda JK, Dusza SW, Navarrete-Dechent C, Liopyris K, Marghoob AA, Marchetti MA. Incidence of New Primary Cutaneous Melanoma in Patients With Metastatic Melanoma Treated With Immune Checkpoint Inhibitors. *JAMA Dermatology*. 2021;157(1):79. DOI:10.1001/jamadermatol.2020.3671. PMID: 32936222. PMCID: PMC7495326.

9. Lallas A, Apalla Z, Kyrgidis A, et al. Second primary melanomas in a cohort of 977 melanoma patients within the first 5 years of monitoring. *J Am Acad Dermatol*. 2020;82(2):398-406. DOI:10.1016/j.jaad.2019.08.074. PMID: 31499156.