Resolution of paraneoplastic alopecia areata following nivolumab in a patient with metastatic melanoma

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INTRODUCTION

Alopecia areata (AA) is an autoimmune disorder resulting in premature hair shedding in discrete patches.[1] The precise immune targets within the hair follicle are unknown but are suggested to be antigens associated with keratinocytes[2] or melanocytes.[3,4] Induction triggers of AA include viruses, infections, and other inflammatory states.[5]

Here, we report an unusual case of paraneoplastic AA that developed at the onset of stage IIIC melanoma progression. This patient's AA was refractory to standard treatments but quickly resolved after initiation of adjuvant nivolumab, an anti-programmed cell death protein 1 immune-checkpoint inhibitor used to treat advanced melanoma. Interestingly, affected areas of his scalp regrew with persistently depigmented hairs without associated vitiligo of the skin. Immune-checkpoint inhibitor therapies are known to induce or exacerbate autoimmune diseases, including vitiligo, thyroid dysfunction, and even AA.[6] The resolution of this patient's paraneoplastic AA after immunotherapy suggests that autoimmune conditions may paradoxically resolve with successful treatment of their underlying cancer. Additionally, this unique case describes the concomitant onset and resolution of AA with metastatic melanoma, providing a strong associative link between melanocytic antigens in the hair follicle and AA pathogenesis.

Abbreviation used:

AA: alopecia areata

CASE REPORT

A 48-year-old man with a history of stage IA melanoma of the lateral aspect of the right side of the abdomen (treated with wide local excision and subsequent re-excision because of narrow margins) presented to dermatology 2 years later with new-onset progressive hair loss. On examination, he had scattered, round, well-defined areas of nonscarring alopecia on his scalp (Fig 1, *A*). He was diagnosed with new-onset AA and treated with topical and intralesional steroids as well as topical minoxidil for 4 months without benefit. No hair loss, skin depigmentation, or hair pigment changes were noted elsewhere on the body.

At hair loss onset, he also noted unexplained weight loss, right axillary lymphadenopathy, and a nodule on the right side of the chest. Biopsy confirmed *BRAF* V600E metastatic melanoma. Positron emission tomography–computed tomography demonstrated multiple enlarged lymph nodes without evidence of distant disease. This was thought to be a progression of his original pT1a melanoma because of its close anatomic proximity and lack of other primary melanomas on examination. He underwent complete

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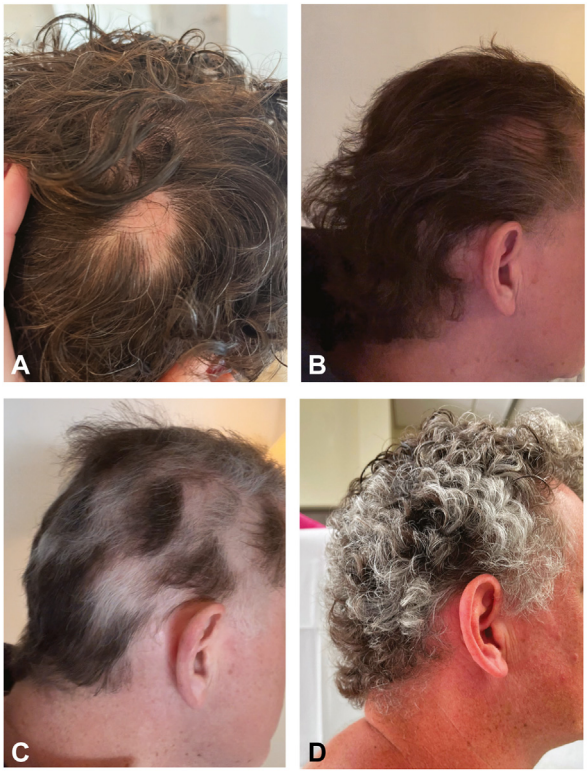

Fig 1. Progression and resolution of paraneoplastic alopecia areata (AA) in a patient with metastatic melanoma. **A,** AA at the time of metastatic melanoma onset. **B,** Worsening of AA 11 weeks later at the time of his cancer surgery and staging, despite topical and intralesional steroid treatments. **C,** Initial regrowth of depigmented hairs in areas of prior AA 6 weeks after the initiation of nivolumab. **D,** Resolution of AA with regrowth of persistently depigmented hair 6 months after initiating nivolumab, coinciding with melanoma disease control.

right axillary lymphadenectomy, with 11/51 positive nodes (stage IIIC). Dermatopathology noted the tumors to be pigmented and diffusely positive for Mart-1, HMB45, S100, SOX10, and tyrosinase. One month later, he received adjuvant radiation to his axilla with a plan to initiate adjuvant nivolumab (240 mg intravenous biweekly) 2 months later. During this time, his hair loss worsened (Fig 1, *B*), and he was counseled that nivolumab would likely further exacerbate his AA.[6]

However, within 6 weeks of nivolumab, the patient surprisingly noted white hair regrowth in all areas affected by AA (Fig 1, *C*). After 4 months, the patient's AA completely resolved with depigmented hair at prior alopecic patches scattered among his baseline unaffected pigmented hair. No other areas of depigmented skin or hair were noted. By 6 months, the full length of involved hairs remained depigmented, his hair regained normal thickness and texture, and his melanoma remained in remission (Fig 1, *D*). At 10 months, pigmented hair began to regrow in previously affected areas, but full-length white hairs remained. The patient now remains disease-free after completion of 1 year of nivolumab and has not had AA recurrence or any immune-related adverse events.

DISCUSSION

Paraneoplastic AA has been documented sparsely in other cancers,[7] and this report describes a case of paraneoplastic AA associated with metastatic melanoma. One case of melanoma-associated AA was previously described in 1978 as Vogt-Koyanagi-Harada syndrome when a 57-year-old woman developed AA, scattered poliosis, uveitis, and hypomelanosis 9 months after surgical resection of her metastatic melanoma. Despite a poor prognosis at the time, the patient remained disease-free after 8 years. The authors postulated that she had developed immunity to her melanoma as reflected by new-onset autoimmune destruction of melanin-containing tissues in the hair follicle, uvea, and skin.[8]

Similarly, we hypothesized that our patient's melanoma recurrence induced immune sensitization of melanocytic antigens in the hair follicle. Clinically, this patient's hair regrew white in affected areas and persisted as depigmented hair. Although transient hypopigmented hair regrowth in alopecia is a phenomenon described in approximately 5.08% to 29.4% of patients with AA,[9,10] depigmentation beyond a few weeks to months is thought to be rare.[3] The persistence of depigmentation in this patient suggests autoimmune destruction of hair follicle melanocytes.[11] His lack of skin depigmentation or ocular symptoms further support the involvement of a shared antigen specific to melanocytes in the hair follicle, rather than epidermal or uveal melanocytes.

If AA can indeed be because of autoimmune T-cell reactivity to hair follicle melanocytes, it remains curious as to why many patients with melanoma develop vitiligo but not AA. Although the immune-privileged environment of the hair follicle may largely explain this, our patient's lack of vitiligo suggests that some melanoma-associated antigens may be unique to follicular melanocytes, which can retain a "stem-like" phenotype and express unique markers. Melanocyte stem cells at the hair bulge replenish pigment-producing mature melanocytes of the hair bulb during anagen, which lends the hair shaft its color.[12] A complex and symbiotic relationship exists between melanocyte stem cells and epithelial stem cells of the hair follicle mediated by several key transcription factors, some

of which are also implicated in the development and progression of melanoma as well as hair loss.[12-14] Identifying shared autoantigens between follicular melanocytes and melanoma may help unlock additional insight into successful therapeutic responses.

Although we suspect the resolution of this patient's paraneoplastic AA was because of nivolumab, we cannot exclude that surgical clearance and/or radiation were instigators. On examining the timeline, his AA worsened in the 2 months following surgery (before nivolumab initiation), despite ongoing conventional AA treatments. His AA began noticeably resolving 6 weeks after the first nivolumab dose and continued to fully regrow despite cessation of AA therapies. We suspect that nivolumab further augmented the immune response against his follicular melanocytes, resulting in their destruction and ultimate restoration of hair growth.

Although we had falsely anticipated that this patient's AA would worsen after nivolumab,[6] this case demonstrates that paradoxical responses of autoimmune conditions may occur in paraneoplastic settings. The patient's simultaneous onset of AA with his melanoma recurrence and his subsequent depigmented hair regrowth strongly support follicular melanocytic antigens as autoreactive targets in select AA cases. Further investigations are needed into the precise autoepitopes relevant to the biology and treatment of both AA and melanoma, as well as the role of immunotherapy in the resolution of paraneoplastic autoimmune events.

Conflicts of interest

Dr Homsi is an advisory board member for Boehringer Ingelheim. Ms Wix and Dr Gill have no conflicts of interest to declare.

REFERENCES

1. Strazzulla LC, Wang EHC, Avila L, et al. Alopecia areata: disease characteristics, clinical evaluation, and new perspectives on pathogenesis. *J Am Acad Dermatol*. 2018;78(1):1-12. https://doi.org/10.1016/j.jaad.2017.04.1141
2. Wang EHC, Yu M, Breitkopf T, et al. Identification of autoantigen epitopes in alopecia areata. *J Invest Dermatol*. 2016;136(8):1617-1626. https://doi.org/10.1016/j.jid.2016.04.004
3. Asz-Sigall D, Ortega-Springall MF, Smith-Pliego M, et al. White hair in alopecia areata: clinical forms and proposed physiopathological mechanisms. *J Am Acad Dermatol*. 2019. https://doi.org/10.1016/j.jaad.2018.12.047
4. Gilhar A, Landau M, Assy B, Shalaginov R, Serafimovich S, Kalish RS. Melanocyte-associated T cell epitopes can function as autoantigens for transfer of alopecia areata to human scalp explants on Prkdc(scid) mice. *J Invest Dermatol*. 2001;117(6):1357-1362. https://doi.org/10.1046/j.0022-202x.2001.01583.x
5. Ito T. Recent advances in the pathogenesis of autoimmune hair loss disease alopecia areata. *Clin Dev Immunol*. 2013;2013:348546. https://doi.org/10.1155/2013/348546
6. Lakhmiri M, Cavelier-Balloy B, Lacoste C, et al. Nivolumab-induced alopecia areata: a reversible factor of good prognosis? *JAAD Case Rep* 2018;4(8):761-765. https://doi.org/10.1016/j.jdcr.2018.05.022
7. Cogan RC, Perlmutter JW, von Kuster K, Wiseman MC. Paraneoplastic alopecia areata surrounding a low-grade cutaneous carcinoma with squamous and trichoblastic features. *JAAD Case Rep*. Dec 2021;18:8-11. https://doi.org/10.1016/j.jdcr.2021.09.038
8. Sober AJ, Haynes HA. Uveitis, poliosis, hypomelanosis, and alopecia in a patient with malignant melanoma. *Arch Dermatol*. 1978;114(3):439-441.
9. Lee YB, Jun M, Lee WS. Alopecia areata and poliosis: a retrospective analysis of 258 cases. *J Am Acad Dermatol*. 2019;80(6):1776-1778. https://doi.org/10.1016/j.jaad.2018.11.033
10. Lim SH, Kang H, Jung SW, Lee WS. Prognosis in patients with alopecia areata with poliosis: A retrospective cohort study of 479 cases. *Indian J Dermatol Venereol Leprol*. 2023:1-3. https://doi.org/10.25259/IJDVL_552_2022
11. Messenger AG, Bleehen SS. Alopecia areata: light and electron microscopic pathology of the regrowing white hair. *Br J Dermatol*. 1984;110(2):155-162. https://doi.org/10.1111/j.1365-2133.1984.tb07461.x
12. Rabbani P, Takeo M, Chou W, et al. Coordinated activation of Wnt in epithelial and melanocyte stem cells initiates pigmented hair regeneration. *Cell*. 2011;145(6):941-955. https://doi.org/10.1016/j.cell.2011.05.004
13. Chang CY, Pasolli HA, Giannopoulou EG, et al. NFIB is a governor of epithelial-melanocyte stem cell behaviour in a shared niche. *Nature*. 2013;495(7439):98-102. https://doi.org/10.1038/nature11847
14. Takeo M, Lee W, Rabbani P, et al. EdnrB governs regenerative response of melanocyte stem cells by crosstalk with Wnt signaling. *Cell Rep*. 2016;15(6):1291-1302. https://doi.org/10.1016/j.celrep.2016.04.006