Nivolumab-induced alopecia areata: A reversible factor of good prognosis?

Myriam Lakhmiri, MD,[a,b,c] Bénédicte Cavelier-Balloy, MD,[d] Caroline Lacoste, MD,[d]
Charles Cassius, MD, MSc,[e] Barouyr Baroudjian, MD,[a] Julie Delyon, MD, MSc,[a,f,g]
Céleste Lebbé, MD, PhD,[a,f,g] and Pascal Reygagne, MD[b]

Paris, France, and Rabat, Morocco

Key words: alopecia areata; anti−programmed cell death protein-1; drug adverse event; immune related; lung cancer; melanoma; nivolumab.

INTRODUCTION

Immune checkpoint inhibitors (ICI) are new therapies used for solid and hematologic cancers.[1,2] They induce activation of CD4 and CD8 cells that target tumor cells and may target unidentified cutaneous antigens, resulting in an inflammatory process after cross-reaction with normal antigens and in immune-related adverse events.[3] Skin toxicity seems to be higher with monoclonal antibody targeting the cytotoxic T-lymphocyte−associated antigen-4 (CTLA-4) compared with monoclonal antibody targeting programmed cell death protein-1 (PD-1).[3] Used in combination, cutaneous immune-related adverse events would be more prevalent and more severe.[3] Maculopapular rash, lichenoid reactions, pruritus, vitiligo, bullous disorders, and psoriasis exacerbation, among others, are related.[3] One percent to 2% of the patients go on to have alopecia areata (AA) or universalis.[3] We report 4 cases of AA after treatment with nivolumab (anti−PD-1) alone or in combination with ipilimumab (anti−CTLA-4), for metastatic melanoma and lung cancer.

CASE REPORTS

Case 1

A 54-year-old woman with lung adenocarcinoma and carcinomatous lymphangitis was treated with nivolumab in January 2016, after 3 lines of chemotherapies (including cisplatin, pemetrexed, bevacizumab, carboplatin, paclitaxel and trastuzumab, from September 2013 to October 2015). In July

Abbreviation used:	
AA:	alopecia areata
CTLA-4:	cytotoxic T-lymphocyte−associated antigen-4
ICI:	immune checkpoint inhibitors
PD-1:	programmed cell death protein-1
PD-L1:	programmed death ligand-1

Fig 1. Nivolumab-induced AA before treatment in metastatic lung cancer (case 1).

2016, after 9 infusions, alopecic patches appeared on the scalp evolving to universal alopecia in October 2016 (Fig 1). Dermoscopy found yellow and black dots and anisotrichia (Fig 2). Biopsy of the scalp found a follicular miniaturization and a moderate superficial fibrosis without inflammation. Treatment included clobetasol gel and foam then intralesional triamcinolone. No regrowth of hair or vitiligo were noted after 9 months of follow-up.

Fig 2. Dermoscopy shows yellow and black dots and anisotrichia in nivolumab-induced AA used for metastatic lung cancer (case 1).

Fig 4. Dermoscopy shows yellow and black dots, anisotrichia, and poliosis in nivolumab-induced AA before treatment in lung cancer (case 2).

Fig 3. A, Nivolumab-induced AA before treatment in metastatic lung cancer (case 2). B, Nivolumab-induced AA regrowth after 3 months of treatment (case 2).
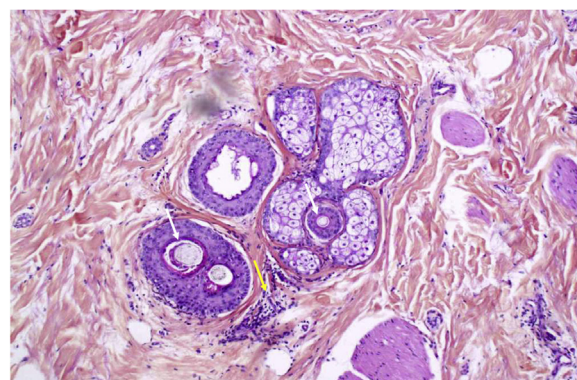

Fig 5. Histology shows perifollicular lymphocytic infiltrate and a follicular miniaturization in nivolumab-induced AA used for metastatic lung cancer (case 2).

anisotrichia (Fig 4). The scalp biopsy found a light perifollicular lymphocytic infiltrate, a follicular rarefaction and miniaturization, and an important increase in telogen/anagen ratio (Fig 5). Foam and shampoo corticosteroid was given in February 2017. A regrowth of hair with poliosis appeared after 1 month and persisted after 3 months of follow-up (Fig 3, B) with no vitiligo. Nivolumab was continued. The cancer was still in remission in March 2018, 30 months after introduction of nivolumab.

Nivolumab was pursued. The cancer was still controlled in April 2018, 26 months after introduction of nivolumab.

Case 2

A 64-year-old woman with lung adenocarcinoma was treated with chemotherapies (carboplatin and pemetrexed then erlotinib then docetaxel) from February 2010 to June 2013. The tumor recurred in June 2015 with metastatic pulmonary nodules, and nivolumab was started in September 2015. In December 2016, the patient presented with an extensive alopecia of the scalp (grade 2) (Fig 3, A). Dermoscopy found black and yellow dots with

Case 3

A 29-year-old woman presented a wild-type *BRAF* metastatic melanoma and received 4 infusions of ipilimumab and nivolumab from January to March 2017. Treatment was followed by maintenance with nivolumab in association with localized radiotherapy of a bone metastasis for analgesic purposes. The patient went on to have vitiligo on the trunk and legs and hair loss (grade 2) in May 2017. Areas of alopecia were well circumscribed on the scalp (Fig 6, A), and dermoscopy found yellow and black dots, anisotrichia, and poliosis (Fig 7). Scalp biopsy found a

Fig 6. A, Nivolumab-induced AA before treatment in metastatic melanoma (case 3). **B**, Nivolumab-induced AA regrowth after 9 months of treatment (case 3).
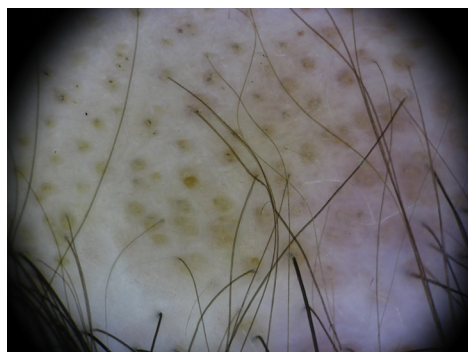

Fig 7. Dermoscopy shows yellow and black dots, anisotrichia, and poliosis in nivolumab-induced AA after treatment in metastatic melanoma (case 3).
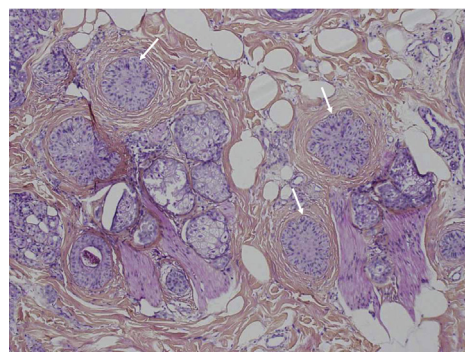

Fig 8. Histology shows a miniaturization of hair with telogen follicles with a slight perifollicular lymphocytic infiltrate in nivolumab-induced AA used for metastatic melanoma (case 3).

miniaturization of hair with telogen follicles with a slight perifollicular lymphocytic infiltrate (Fig 8). Treatment was based on topical corticosteroid cream and shampoo then intralesional injections of triamcinolone. In January 2018, almost complete regrowth of hair with poliosis was noted (Fig 6, B). Nivolumab was continued. In April 2018, the melanoma was in partial remission, 15 months after introduction of nivolumab.

Case 4

A 33-year-old woman with *BRAF*-mutated metastatic melanoma was treated with ipilimumab and nivolumab from August 2017 because of disease progression after 7 months of *BRAF* and *MEK* inhibitors. After the third infusion of ipilimumab and nivolumab, 2 noncicatricial alopecia patches typical of AA appeared on the scalp (Fig 9, A and B). Dermoscopy was typical with yellow and black dots and tapering hairs at the periphery of the patches. She was treated with topical corticosteroid cream. Partial regrowth of hair with poliosis was noted 3 months later with no vitiligo. Nivolumab was not discontinued. In March 2018, melanoma was in complete remission, 14 months from diagnosis and 8 months from introduction of nivolumab.
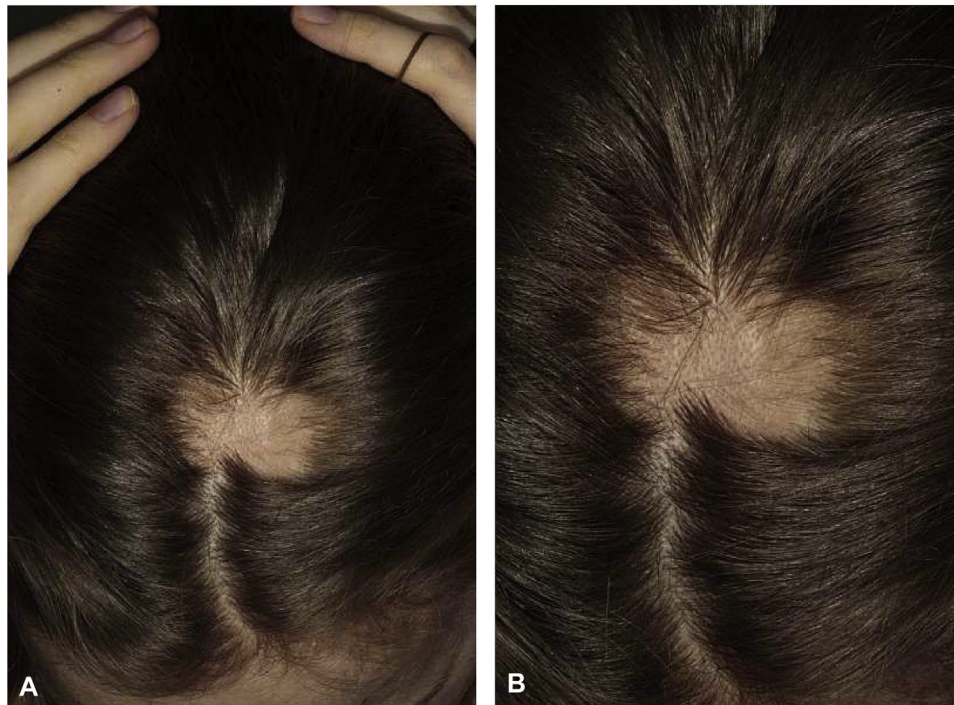
Fig 9. A and **B**, Nivolumab-induced AA before treatment in metastatic melanoma. Clinical photographs show a typical patch of AA (case 4).

DISCUSSION

AA is a rare side effect of ICI. The first case was reported in 2006, and at least 24 cases have been reported so far[4,5]: 18 cases with anti−PD-1, 2 cases with anti−CTLA-4, 3 cases with both anti−PD-1 and anti−CTLA-4, and 1 case with monoclonal antibodies targeting programmed death ligand-1 (PD-L1).

AA is an acquired autoimmune disease, which can be associated with other autoimmune disorders (eg, vitiligo, thyroiditis, and type 1 diabetes). The diagnostic is clinical: areas of alopecia are well defined, localized, or diffuse and nonscarring. Many and regular yellow dots, black dots, and short vellus hair are evocative in dermoscopy. Histology is necessary in case of doubt and is characterized with a peribulbar lymphocytic inflammation of variable intensity in acute stage, a miniaturization of follicles, and an inversion of telogen/anagen hair ratio during subacute and chronic stages. Fibrosis develops in more chronic stages, and the alopecia can become cicatricial and permanent,[6] and this is what probably happened in our first case. Poliosis is common at the onset of the regrowth.[4]

In our cases, clinical, dermoscopic and histologic data were in agreement with the diagnosis of AA. They were likely related to nivolumab, known to induce immune-related adverse events, and given in the delay of a few months between their introduction and the occurrence of the hair loss (2, 4, 6, and 15 months). AA pathogenesis remains unclear, and only fully pigmented anagen hairs seem to be concerned. It is suggested that melanogenesis associated autoantigens are targeted by perifollicular CD8 T cells.[7] ICI-induced vitiligo appears after the destruction of melanocytes[8] and is associated with good response to treatment in melanoma.[3] In case 3, there was an AA, a vitiligo, and a good response to nivolumab. In cases 1, 2, and 4, there was an AA with no vitiligo, and the response to nivolumab was good.

In the light of these data and according to the good response observed in our 4 patients, we hypothesize that nivolumab-induced AA would be another factor of good prognosis not necessarily related to vitiligo and associated with durable response to ICI. More data are necessary to confirm this hypothesis. Furthermore, we can hypothesize that targeted melanogenesis-associated autoantigens are common in ICI-induced alopecia and in ICI-induced vitiligolike conditions. The use of melanocytic markers on skin and hair biopsies during ICI treatment may reveal more on the effects of these drugs on melanocytes and the link to AA and vitiligo. Considering the increasing use of ICI, practitioners should know about the possibility of immune-related alopecia, which can be reversible with topical or intralesional corticosteroids while the ICI is not discontinued.

REFERENCES

1. Azoury SC, Straughan DM, Shukla V. Immune checkpoint inhibitors for cancer therapy: clinical efficacy and safety. *Curr Cancer Drug Targets*. 2015;15:452-462.
2. Tsirigotis P, Savani BN, Nagler A. Programmed death-1 immune checkpoint blockade in the treatment of hematological malignancies. *Ann Med*. 2016;48:428-439.
3. Sibaud V. Dermatologic reactions to immune checkpoint inhibitors: skin toxicities and immunotherapy. *Am J Clin Dermatol*. 2018;19:345-361.
4. Zarbo A, Belum VR, Sibaud V, et al. Immune-related alopecia (areata and universalis) in cancer patients receiving immune checkpoint inhibitors. *Br J Dermatol*. 2017;176:1649-1652.
5. Weber JS, Hodi FS, Wolchok JD, et al. Safety profile of nivolumab monotherapy: a pooled analysis of patients with advanced melanoma. *J Clin Oncol*. 2017;35:785-792.
6. Werner B, Mulinari-Brenner F. Clinical and histological challenge in the differential diagnosis of diffuse alopecia: female androgenetic alopecia, telogen effluvium and alopecia areata - Part II. *Anaisbrasileiros de dermatologia*. 2012;87:884-890.
7. McElwee KJ, Gilhar A, Tobin DJ, et al. What causes alopecia areata? *Exp Dermatol*. 2013;22:609-626.
8. Harris JE. Vitiligo and alopecia areata: apples and oranges? *Exp Dermatol*. 2013;22:785-789.