

Remote-Onset Alopecia Areata Attributed to Ipilimumab

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PRACTICE POINTS

- Cutaneous immune-related adverse effects (irAEs) are among the most common adverse effects of ipilimumab, a fully humanized monoclonal antibody directed against cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) used to treat advanced-stage melanoma.
- Alopecia areata is a rarely reported irAE, but its connection to CTLA-4 dysregulation may mean that clinicians see an increased incidence at higher ipilimumab doses.

Ipilimumab is a fully humanized monoclonal antibody against cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and one of a growing class of immunomodulatory therapies for melanoma. The most common toxicities are immune-related adverse effects (irAEs), which manifest most frequently in the skin as rash and pruritus. We report a case of alopecia areata (AA) attributed to ipilimumab that presented 1.5 years after treatment. Because CTLA-4 dysregulation has been increasingly linked to AA, the incidence of this irAE may increase following US Food and Drug Administration approval of a higher dose of ipilimumab for adjuvant treatment of stage III melanoma.

Cutis. 2019;104:E25-E27.

Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) is a key co-stimulatory receptor expressed on activated T cells that negatively regulates T-cell activation.¹⁻³ It exerts its effects in part by the prevention of IL-2 transcription and inhibition

of cell-cycle progression.⁴ Cytotoxic T-lymphocyte-associated antigen 4 also is expressed by a subset of CD25⁺CD4⁺ regulatory T cells (Tregs), where it plays a role in immune tolerance.⁵ Blockade has demonstrated antitumor activity as well as immune activation, and CTLA-4 dysregulation has been implicated in autoimmune diseases such as alopecia areata (AA).⁶

Ipilimumab is a fully humanized monoclonal antibody against CTLA-4 and one of a growing class of immune checkpoint inhibitor therapies for metastatic melanoma. Phase 2 and 3 clinical trials have shown an improved survival effect of ipilimumab in patients with advanced melanoma,⁷⁻¹⁰ with 3-year survival rates ranging from 20.8% to 46.5%.^{10,11} The US Food and Drug Administration approved ipilimumab in 2011 for treatment of unresectable or metastatic melanoma.¹² The most common toxicities of ipilimumab are immune-related adverse effects (irAEs), which represent loss of tolerance to self-antigens.¹³ Immune-related adverse effects occur in 64.2% of patients,¹⁴ with severe or life-threatening irAEs in 17.8% of patients.¹⁴ Rates of irAEs appear dose dependent but consistent across increased doses.¹⁵ Cutaneous irAEs occur in more than 47% of patients¹⁶ and commonly manifest as pruritus with or without a diffuse morbilliform rash,^{10,17} though less common skin reactions, including vitiligo, vasculitis, and Stevens-Johnson syndrome/toxic epidermal necrolysis, have been documented.^{9,18}

Generalized AA and its more widespread variant, alopecia universalis, have been reported as adverse effects of ipilimumab monotherapy in 2 prior cases in the English-language literature (Table).^{17,19} Alopecia areata also has been attributed to combination immune checkpoint inhibitor therapy.^{20,21} We report a case of

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Review of Demographics and Clinical Metrics of Reported Cases of Alopecia Areata Attributed to Ipilimumab

Reference (Year)	Patient Age, y/ Gender	Melanoma Stage ^a	Clinical Appearance	Ipilimumab Dose, mg/kg	Onset	Associated Immune-Related Adverse Effects
Jaber et al ¹⁷ (2006)	34/M	IV	Generalized alopecia involving scalp, face, and trunk	5	Following dose 3	Rash, pruritus
Assi and Wilson ¹⁹ (2013)	54/M	IV	Alopecia universalis	10	Following dose 3	Vitiligo, hypophysitis
Current report	90 ^b /M	IV	Alopecia localized to scalp	3	1.5 y after treatment	Rash, pruritus, subclinical hyperthyroidism

Abbreviation: M, male.

^aBased on the American Joint Committee on Cancer staging system.

^bAge at onset of alopecia.

AA attributable to ipilimumab monotherapy that was localized exclusively to the scalp and remote in onset following treatment.

Case Report

An 88-year-old man with pT3bpN3 nodular melanoma of the back demonstrated multiple lung metastases by positron emission tomography–computed tomography. Lactate dehydrogenase was within reference range, and his Eastern Cooperative Oncology Group performance status was 0 (fully active). One month later, he was started on ipilimumab 3 mg/kg intravenous infusion every 3 weeks for a total of 4 doses. At approximately week 6, his course was complicated by mild fatigue, a faintly erythematous morbilliform rash, and mild pruritus, with laboratory evidence of subclinical hyperthyroidism. Follow-up positron emission tomography–computed tomography at the conclusion of treatment demonstrated complete regression of previously noted hypermetabolic foci. His symptoms and subclinical hyperthyroidism resolved several months later.

Seventeen months after completion of ipilimumab therapy (at age 90 years), the patient's barber noted new-onset hair loss on the right occipital scalp. Physical examination demonstrated a well-circumscribed patch of nonscarring alopecia (approximately 6 cm) that was clinically consistent with AA (Figure). There were no associated symptoms or other involved areas of hair loss. He denied any personal or family history of AA. The patient's melanoma has remained in remission to date.

Comment

This case is unique in that AA was localized to a single circumscribed patch on the scalp and occurred nearly 1.5 years after treatment with ipilimumab, which may



Well-circumscribed, nonscarring alopecia (6 cm) on the right occipital scalp consistent with alopecia areata.

indicate a robust blockade of CTLA-4 given the remote development of autoimmunity in the setting of persistent remission of melanoma. Although the appearance of AA may be coincidental, onset at 90 years of age would be unusual. The mean age of onset of AA has been reported between 25.2 and 36.3 years,^{22,23} and its incidence in men older than 60 years is only 6.4 per 100,000 person-years.²⁴

Although AA is a rare irAE of CTLA-4 blockade, the disease has been increasingly linked to CTLA-4 dysregulation in both animal models and humans.^{6,25,26} A genome-wide association study of 1054 patients with AA and 3278 controls implicated several genes controlling activation and proliferation of Tregs, including CTLA-4.²⁷ More specifically, single-nucleotide polymorphisms of the CTLA-4 gene were found to be

associated with AA in a study of 1196 unrelated patients and 1280 controls,²⁸ and Megiorni et al²⁹ identified a single-nucleotide polymorphism of CTLA-4, CT60, as a contributory genetic determinant of AA in Italian patients.

Given the role of CTLA-4 dysregulation in the pathogenesis of AA, the very low rates of AA in ipilimumab are somewhat surprising, which may represent a reporting bias. Alternatively, there may be sufficient Treg activity to prevent high rates of AA at a lower ipilimumab dose of 3 mg/kg but insufficient activity to prevent development of other irAEs. With US Food and Drug Administration approval of ipilimumab at a higher dose of 10 mg/kg for use as adjuvant therapy for stage III melanomas,¹² less common cutaneous irAEs such as AA may be seen with increased frequency. Clinicians planning ipilimumab therapy should discuss this side effect and other potential irAEs with their patients before initiation of treatment.

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