

Alopecia areata after mogamulizumab treatment



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INTRODUCTION

In 2018, the anti-CC chemokine receptor-4 (CCR4) monoclonal antibody mogamulizumab was approved to treat patients with mycosis fungoides (MF) and Sézary syndrome (SS) with disease refractory to systemic therapy.¹ Clinically, mogamulizumab has been highly effective, but side effects remain common.¹ The most frequent side effect is the development of heterogeneous rashes, collectively known as “mogamulizumab-associated rash”, which includes several clinical phenotypes—papules/plaques, folliculotropic MF-like plaques, and cutaneous granulomatous drug eruption.^{2,3}

CCR4 is found on the surface of malignant CD4⁺ cells in cutaneous T-cell lymphoma, in addition to healthy T-helper (Th) 2 cells and regulatory T (T_{reg}) cells.⁴ Thus, as one might expect, adverse reactions to mogamulizumab mimic immunologic disease.⁴ As mogamulizumab utilization increases across specialty dermatology clinics, reports of significant adverse events become more salient and may provide guidance for management (eg, prevent premature discontinuation of therapy). Here we describe the development of alopecia areata (AA) universalis after mogamulizumab therapy.

CASE REPORT

A 42-year-old woman with no personal or family history of autoimmune illness presented with erythroderma and intractable pruritus. A diagnosis of SS was made after skin biopsy and flow-cytometry showed a CD4/CD8 ratio of 9 with loss of CD7 and CD26 expression. She was refractory to bexarotene therapy, and subsequent treatment with

Abbreviations used:

AA:	alopecia areata
CCR4:	CC chemokine receptor 4
MF:	mycosis fungoides
SS:	Sézary syndrome

mogamulizumab resulted in prompt disease remission. Approximately 16 months after beginning mogamulizumab, she experienced rapidly progressive hair loss. Physical exam at the time revealed well-demarcated patches of alopecia on the back of the scalp (Fig 1, A) with preserved follicular ostia. Mogamulizumab was subsequently held due to the patient's concern for substantial hair loss. Through a shared-decision making approach, the patient and care team chose to pursue active surveillance and did not initiate any other anti-neoplastic therapies. Over the next 3 months, her SS remained quiescent, but she progressed to total body hair loss, including loss of eyebrows, eyelashes, axillary, and pubic hair (Fig 1, B). Clinically, these features were strongly compatible with AA universalis. Nonetheless, a punch biopsy of the groin with vertical and horizontal sectioning was performed to rule out other etiologies of alopecia. Histopathology of the specimen revealed findings consistent with chronic AA, as evidenced by a greatly reduced follicle count with all follicles in telogen phase. There was no evidence of active lymphoma. Her hematologic workup, including complete blood cell count with differential, was unremarkable. To combat the alopecia, she was treated with monthly 10 mg/mL intralesional triamcinolone to the eyebrows, and she experienced

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Fig 1. **A**, Well-demarcated patches of alopecia on the posterior aspect of the scalp. **B**, Progression to total scalp hair loss. **C**, Hair regrowth.

full eyebrow regrowth after 6 months of therapy. On the scalp, she deferred injections, until spontaneous patchy hair regrowth was noted, then had monthly 5-mg/mL injections to alopecic patches on the scalp for 3 months. She was also prescribed topical clobetasol 0.05% ointment to use for patchy areas of scalp alopecia, which she used intermittently. She achieved full scalp and eyebrow hair regrowth after 13 months (Fig 1, C).

DISCUSSION

Despite being ubiquitous in dermatology clinics, AA is still poorly understood as both a primary disease and when occurring as a drug side effect. Several reports have noted AA occurring after monoclonal antibody therapy for solid tumors, specifically programmed cell death protein 1 blockade.⁵ The impact of AA development on prognosis is still under investigation, but certain studies suggest that immune-related adverse events could predict better cancer-related outcomes.⁶ Our case provides further insight into potential immunologic mechanisms underlying this interesting disease in the setting of targeted antibody treatment for hematologic malignancy.

Mogamulizumab is believed to produce its intended effect via antibody-dependent cell-mediated cytotoxicity targeted toward cells expressing surface CCR4, which includes Th2 and T_{reg} cells.^{1,4} In advanced MF/SS, CCR4-expressing T-cells are thought to display a Th2 phenotype.⁴ Preferential depletion of Th2-polarized cells may lead to unopposed Th1-mediated inflammation and resultant overexpression of Th1 cytokines (ie, interferon gamma).²

In addition to disrupting the Th1/Th2 inflammatory axis, mogamulizumab also likely disrupts T_{reg} cell homeostasis. T_{reg} cells serve to provide a

key restraint to the development of autoimmunity.⁷ As an example, a recent study found that suppressive FOXP3⁺/CD39⁺ T_{reg} cells were significantly reduced in both peripheral blood and lesions of patients with primary AA.⁸ Numerous reports have demonstrated mogamulizumab's ability to non-specifically deplete T_{reg} cells in peripheral blood via antibody-dependent cell-mediated cytotoxicity.⁴ This mechanism has been implicated in the development of other autoimmune phenomena such as vitiligo, hepatitis, and thyroiditis, which may occur between 2 months up to 3 years after first mogamulizumab infusion.^{9,10} Taken together, these observations suggest that the AA observed here is most likely to be a consequence of absent T_{reg} cell-mediated inhibition of an autoimmune attack, secondary to mogamulizumab. We cannot definitively rule out that this finding may be coincidental, although it is unlikely given the overall low prevalence of AA universalis and lack of autoimmune illness in this patient or her family.

A detailed mechanistic basis for mogamulizumab-associated alopecia remains to be elucidated. When alopecia is encountered during anti-CCR4 therapy for MF/SS, pertinent workup includes obtaining a focused history (ie, presence of pruritus, B-symptoms) and inspecting (+/- biopsy) problematic areas to rule out progression of disease. Larger observational studies of the impact of mogamulizumab-induced cutaneous adverse events, such as AA, could inform providers of their prognostic significance. Additional reports of successful treatment strategies for mogamulizumab-associated alopecia, including the experience of novel steroid-sparing immunosuppressives, such as topical or systemic tofacitinib, may provide benefit to future patients.

Conflicts of interest

Drs Musiek and Shah serve on the advisory board of Kyowa Kirin. Mr Raval, Ms Alexander, Ms Monnin, and Drs Yokoyama and Rosman have no conflicts of interest to declare.

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