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Case Report

Vitiligo following alemtuzumab therapy in multiple sclerosis: a demonstration of secondary autoimmunity

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ABSTRACT

Secondary autoimmunity is the most frequent adverse event that occurs in Relapsing and remitting multiple sclerosis (RRMS) patients who are being treated with alemtuzumab, however there have been few reported cases of autoimmune dermatologic conditions associated with alemtuzumab therapy. We report a case of a patient with RRMS who presented with depigmentation of the right lower cutaneous lip, consistent with vitiligo, seven months after her second treatment cycle with alemtuzumab. We emphasize the need for careful clinical surveillance of patients undergoing alemtuzumab therapy for rarely described secondary cutaneous autoimmune diseases.

Keywords: Vitiligo, Alemtuzumab, Depigmentation, Multiple sclerosis, Adverse events, Secondary autoimmunity

INTRODUCTION

Development of secondary autoimmune conditions is a frequent adverse event that occurs in Relapsing and remitting multiple sclerosis (RRMS) patients who are being treated with alemtuzumab, however there have been few reported cases of autoimmune dermatologic conditions associated with alemtuzumab therapy.[1-4] We report a case of a patient with RRMS who developed vitiligo seven months after her second treatment cycle with alemtuzumab. We emphasize the need for careful clinical surveillance of patients undergoing alemtuzumab therapy for development of rarely described secondary cutaneous autoimmune diseases.

CASE REPORT

A 54-year-old caucasian female undergoing therapy with alemtuzumab for Relapsing and remitting multiple sclerosis (RRMS) presented with new onset perioral hypopigmentation. Her personal and family history excluded any other autoimmune diseases besides RRMS. Seven months after her second cycle of alemtuzumab, the patient noted new depigmented patches on her right lower cutaneous lip. She denied having similar symptoms previously. Physical examination, including woods lamp examination, demonstrated well demarcated depigmentation of the cutaneous lip, consistent with vitiligo. No evidence of depigmentation was present elsewhere on the body including hands or genitalia. The patient had been monitored closely by neurology, with all ancillary tests without abnormalities. Treatment with topical tacrolimus was initiated.

DISCUSSION

Vitiligo is an autoimmune disorder which progressively destroys melanocytes leading to depigmentation of the

skin, mucosa and hair.[5] The pathogenesis of vitiligo is unknown; however, it is hypothesized to be a largely T-cell driven autoimmune disorder, with autoreactive melanocyte-specific CD8+ T cells responsible for melanocyte destruction.[6-8] Upon histopathological evaluation, early lesions of vitiligo demonstrate infiltrate of CD8+ T-cells, while later lesions demonstrate a perivascular lymphocytic infiltrate.[9] IL17 and IL21 have also been implicated as upregulated in the pathogenesis of vitiligo.[10,11] Vitiligo is commonly associated with other autoimmune conditions, but has not been commonly reported in association with multiple sclerosis, however shared HLA haplotypes including HLA-RB1 or HLA-DQB1 may confer increased disease risk in susceptible individuals.[8,12,13] One case series of 3 patients and one case report describe development of vitiligo in four RRMS patients being treated with alemtuzumab.[1,4] Similar to our patient, these cases describe onset of vitiligo symptoms after 5, 14, 18, and 52 months following alemtuzumab initiation.[1,4] Our patient presented with only focal vitiligo; other reported patients experienced more generalized disease.[1,4]

Alemtuzumab is a humanized monoclonal IgG1 antibody which binds CD52 protein, a surface molecule primarily expressed on B and T cells.[2,14,15] Alemtuzumab causes rapid sustained depletion of CD52+ cells, followed by slow repopulation of cells arising from unaffected hematopoietic precursors cells.[16] Despite high proven efficacy, alemtuzumab is associated with considerable risks including autoimmune diseases in 47% patients with peak incidence within five years of treatment.[17-20] Secondary autoimmune diseases predominantly include thyroid disorders (35-41%) and immune thrombocytopenia(3-3.5%).[17,18,21,22] The few published cases of autoimmune dermatologic conditions related to treatment with alemtuzumab include one retrospective case series reporting 3 cases of vitiligo, one case report of vitiligo with keobnerization, and one report of alopecia universalis.[1,3,4]

The underlying pathophysiologic causes of these secondary autoimmune conditions is largely unknown; there has been debate on the culprit role of B-cells vs T-cells in these conditions. B-cells have been assumed to be the central drivers of these secondary immune reactions, as there is a predominance of anti-body medicated autoimmune disorders; however, an argument for the role of T-cells has been proposed as well. [4,16,21-23] It has been speculated that depletion of CD52 CD4+ regulatory T cells may be contributory to the onset of these conditions. [22,23] The B-cell lymphocytic population recovers more rapidly than the regulatory T cell population, which may lead to immune dysregulation.[24,25] This has led to the hypothesis that the loss of balance between regulatory T-lymphocytes and B-lymphocytes contributes to the development of vitiligo in patients being treated with alemtuzumab.[1] An alternative hypothesis highlights the role of IL-21; IL-21 has been demonstrated to drive proliferation of effector memory T-cells in autoimmunity following alemtuzumab.[26] As IL-21 has also been implicated in pathogenesis of vitiligo, Reck et al speculate that the increase in IL-21 levels may drive vitiligo development in RMMS patients.[4,11] Also of interest, all of the patients reported by Reck et al expressed at least 2 vitiligo risk alleles (HLA-A*02, HLA-DRB1*03, HLA-DRB1*04, and HLA-DBQ1*03).[4]

We support the hypothesis that the development of vitiligo under these circumstances is a T-cell driven secondary autoimmune condition. We emphasize the need for careful clinical surveillance of patients undergoing alemtuzumab therapy for secondary cutaneous autoimmune diseases and the need for further mechanistic studies to improve knowledge of the pathogenesis of secondary autoimmunity.

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