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Citation

Ahmed, Sarah. 2016. Reduced Incidence of Skin Cancer in Patients With Alopecia Areata: A Retrospective Cohort Study. Doctoral dissertation, Harvard Medical School.

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Reduced Incidence of Skin Cancer in Patients with Alopecia Areata: A Retrospective Cohort Study

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Word count (excluding title, abstract, figures, acknowledgements, and references): 1370

3 Tables

Abstract:

The risk of skin cancer in patients with alopecia areata (AA) is unknown. While the risk of skin cancer in chronic inflammatory alopecias may be elevated, AA shares many characteristics with vitiligo, an autoimmune illness associated with decreased risk of melanoma and non-melanoma skin cancers. In this retrospective cohort study, we determined the risk of developing skin cancer among patients with AA in a validated cohort relative to matched controls at two tertiary care hospitals in Massachusetts. There was a significantly decreased risk of NMSC in AA patients than controls (OR = 0.63, 95% CI = 0.48-0.81). There was a trend towards a protective effect of AA associated with melanoma (OR=0.65, 95% CI = 0.39-1.09). There was no difference in anatomic distribution of skin cancer between patients with AA and controls. Our study demonstrates a decreased risk of nonmelanoma skin cancer and a trend towards reduced risk of melanoma in patients with AA.

Key words: alopecia areata; melanoma; non-melanoma skin cancer; basal cell carcinoma; squamous cell carcinoma; vitiligo; melanocytes; autoimmunity; epidemiology.

Abbreviations used: ARC, Automated Retrieval Console; AA, alopecia areata; BCC, basal cell carcinoma; NMSC, nonmelanoma skin cancer; RPDR, Research Patient Data Repository; SCC, squamous cell carcinoma.

Introduction

Alopecia areata (AA) is an autoimmune disease characterized by patches of non-scarring alopecia. Although the pathogenesis is not completely understood, AA is thought to be a T_H1 -mediated autoimmune disease in which loss of the hair follicle as an immune privileged site results in perifollicular CD8⁺ cytotoxic T cell infiltration [1]. Follicular melanocytes are hypothesized to be a potential antigenic target. This hypothesis is supported by the observation that loss of pigmented hair follicles occurs first, leading to an “overnight greying” phenomenon, followed by initial regrowth of depigmented hair. AA has also been associated with a 3 to 8-fold higher incidence of vitiligo, a skin disorder characterized by autoimmune destruction of melanocytes [2, 3].

Recent studies have demonstrated a decreased risk of melanoma and nonmelanoma skin cancers (NMSC) in vitiligo patients [4]. This protection is thought to be caused by a heightened immune response against melanocyte-specific autoantigens that reduces the likelihood of developing melanoma. The protective effect of vitiligo on NMSC is poorly understood but is theorized to be associated with p53 upregulation in keratinocytes [5].

To date, there is no study that has explored the incidence of skin cancer in patients with AA. However, AA and vitiligo share a similar pathogenesis, in which CD8⁺ T cells and IFN- γ play an active role [6, 7], leading to observed morphological melanosome changes at the hair bulb in AA patients [8]. Given these similarities, we propose that AA may also be protective against skin cancer. Here we determine the relative risk of developing melanoma and NMSC in patients with AA in comparison to matched controls.

Materials and Methods

Study Population

This is a retrospective cohort study of patients in the Research Patient Data Repository (RPDR). The RPDR is a clinical data registry that combines information from 6.5 million patients from the Partners Healthcare System. The RPDR includes patient demographics, diagnoses, medications, pathology reports, and complete longitudinal medical record notes that can be queried for research purposes. We identified and verified diagnosis of 1,796 patients with AA seen between January 1, 2000 and January 1, 2010 using the Automated Retrieval Console (ARC) methodology as described in a prior publication [9]. This project was approved by the Partners Healthcare Institutional Review Board.

We identified controls matched on the following criteria: having a dermatology appointment with a diagnosis of seborrheic dermatitis (ICD-9 690.10) in the RPDR at least once +/- 5 years of study patients' AA diagnosis date; age +/- 5 years; gender; and race. Skin cancer data was obtained by screening all cases and controls for diagnoses of melanoma or non-melanoma skin cancer (ICD-9 172.X and 173.X). The skin cancer diagnoses were verified and location of cancer was recorded by manually reviewing the pathology reports for each case.

Statistical Analysis

Descriptive statistics of the cohort were presented as counts and percents for nominal characteristics, along with mean and standard deviation of age. Propensity score matching was performed to match alopecia areata cases to controls. Propensity scores were estimated from a

logistic regression model predicting AA status from baseline characteristics in Table 1. A greedy 8-1 matching algorithm identified controls, first matching on eight digits of the propensity score, then seven digits, and so on up to a single digit match of propensity score. Odds ratios for incidence of NMSC and melanoma were calculated from generalized estimating equation models.

Among those with NMSC, associations between skin cancer location and AA status were assessed for statistical significance with chi-square tests.

Results

A total of 1,414 cases of AA were identified and matched to 4,242 controls in a 1:3 ratio. The mean age of participants was 46.5 years; 65% were female, and 60.9% were white (Table 1). Skin cancer rates are presented by AA status in Table 2. AA cases were less likely to have NMSC than controls (OR = 0.63, 95% CI = 0.48-0.81). There was a trend towards a protective effect of AA associated with melanoma (OR=0.65, 95% CI = 0.39-1.09). In a sensitivity analysis, 1,768 (98.4%) of all AA patients were matched to a single control. The associations between AA and skin cancer were similar in this sample; AA cases had reduced risk for NMSC (OR = 0.58, 95% CI = 0.43-0.79) as well as lower incidence of melanoma, though non-significant (OR = 0.77, 95% CI = 0.41-1.46).

Location of skin cancer did not significantly differ in cases versus controls (Table 3). Among those with squamous cell carcinoma (SCC), 61.1% of AA cases had SCC on the scalp, head, or neck compared to 47.1% of controls ($p=0.280$), and among those with basal cell carcinoma (BCC), 81.3% of AA cases had BCC on the scalp, head, or neck compared to 71.2% of controls

($p=0.250$).

Discussion

Our study reports the frequency of melanoma and NMSC in a large cohort of AA patients. We found that patients with AA were 37% less likely to develop NMSC than matched controls. Patients with AA also demonstrated a trend toward decreased risk of melanoma, although this did not achieve statistical significance.

These findings are consistent with and extend those from prior reports evaluating skin cancer in vitiligo. A previous study reported a reduction of both NMSC and melanoma in a large cohort of patients with vitiligo [4]. In contrast, other inflammatory types of alopecia have been proposed to increase risk for NMSC. Prior investigations have implicated decreased sun protection from hair loss and chronic inflammation as culprits in the development of NMSC among patients with lichen planopilaris and discoid lupus erythematosus [10, 11].

Our data demonstrates a similar distribution of skin cancer between patients with AA and controls. The universal reduction of skin cancer risk, including areas where there is no alopecia, suggests that the genetics of the patient account for this observation, rather than the active inflammation of AA. The risk reduction of NMSC among patients with AA may therefore provide insight into the role of AA in immune surveillance or molecular repair of damaged cells. Teulings et al hypothesize that patients with vitiligo have protection from actinic damage related to increased levels of p53 expression found in keratinocytes, resulting in decreased NMSC [4]. A similar mechanism might exist in AA.

A potential explanation for decreased melanoma risk in patients with AA may be melanocyte

autoantigens, which are a potential pathologic target in AA. Monoclonal antibodies such as ipilimumab, a CTLA-4 inhibitor intended to potentiate T cell activation has been shown to cause alopecia, as well as vitiligo, and there is evidence to suggest that these autoimmune adverse events are correlated with enhanced tumor regression [12, 13, 14]. Clinical AA may signify a breakdown in T cell tolerance and alteration of a CTLA-4-mediated pathway that primes the system against melanocytes expressed in the hair bulb. Malignant or pre-malignant melanocytes may be compromised by this same mechanism.

These data must be interpreted in the context of the study design. As a multi-center retrospective review of biopsy-proven melanoma and NMSC, our study has a risk of underestimating the number of cases of skin cancer since they may have been diagnosed and treated at sites outside of the Partners Healthcare System. In addition, the study cannot account for NMSC that were ablated with destructive methods and thus never sent for pathology. However, there is no reason to believe that care outside of our system or destruction of NMSC is more or less likely in cases compared to controls. Despite the size of our cohort, the incidence of melanoma was low; a larger study may be necessary to precisely define the risk of melanoma among patients with AA. Prior to matching, there were significant differences in age, gender, and race demographic variables. Propensity score matching was employed in this observational study to minimize bias due to these potential confounders.

In conclusion, we found a 37% reduction of risk of NMSC, and a trend towards a decreased risk of primary melanoma in patients with AA. These results suggest that patients with AA have heightened protection against skin cancer. Larger studies are needed to confirm our findings. These findings allow us to improve our counseling of patients with AA and reinforce the hypothesis of a role for anti-melanocyte autoantigens in patients with AA. In addition, further

elaboration of a possible mechanism may lead to a molecular basis for targeted therapy in the treatment of skin cancer.

Acknowledgement: The authors would like to thank Leila Mostaghimi for her inspiration and for her enthusiasm for our study results. We would also like to thank Helen Kuo with her help in database management.

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Table 1: Participant and Control Group Characteristics After Matching

	Overall 5656 (100.0)	Alopecia Areata 1414 (25.0)	Control 4242 (75.0)	p-value
Age, mean (SD)	46.5 (15.9)	46.4 (15.5)	46.5 (16.0)	0.800
Gender				
Female	3677 (65.0)	900 (63.6)	2777 (65.5)	0.215
Male	1979 (35.0)	514 (36.4)	1465 (34.5)	
Race				
White	3443 (60.9)	858 (60.7)	2585 (60.9)	0.518
Black	877 (15.5)	225 (15.9)	652 (15.4)	
Hispanic	135 (10.4)	135 (9.5)	455 (10.7)	
Other	196 (13.2)	196 (13.9)	550 (13.0)	

p-value from t-test for age, chi-square test for gender and race

Table 2: Skin cancer by alopecia areata status

	n (%) with event	Odds ratio (95% CI)	n (%) with event	Odds ratio (95% CI)
	NMSC		Melanoma	
Alopecia Areata Cases	64 (4.5)	0.63 (0.48, 0.81)	17 (1.2)	0.65 (0.39, 1.09)
Controls	299 (7.0)	1 (Reference)	78 (1.8)	1 (Reference)

CI – confidence interval

Table 3: Location of skin cancer

n (%)	Overall 263 (100.0)	Alopecia Areata 42 (16.0)	Controls 221 (84.0)	p-value
Subtype				
BCC	158 (60.1)	24 (57.1)	134 (60.6)	0.259
SCC	36 (13.7)	9 (21.4)	27 (12.2)	
Both	69 (26.2)	9 (21.4)	60 (27.2)	
Location for patients with SCC (N=105)				
Scalp, head, or neck	52 (49.5)	11 (61.1)	41 (47.1)	0.280
Other locations	53 (50.5)	7 (38.9)	46 (52.9)	
Location for patients with BCC (N=164)				
Scalp, head, or neck	120 (73.2)	26 (81.3)	94 (71.2)	0.250
Other locations	44 (26.8)	6 (18.8)	38 (28.8)	

p-value for chi-square test