

Association of alopecia areata with atopic dermatitis and chronic spontaneous urticaria

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ABSTRACT

Background: Epidemiologic studies report that alopecia areata (AA) is related to various atopic and autoimmune diseases. The purpose of this study was to identify clinical characteristics and the prevalence of comorbid conditions in Israeli patients with AA.

Methods: This retrospective, matched, case-control study was based on data from an electronic patient record data base. The patients with an electronically documented diagnosis of AA were included in the AA group. The control group was randomly sampled from the remaining subjects, with a case-to-control ratio of two controls for each case. Comorbidity was compared between the study groups.

Results: A total of 1751 subjects (49.4% men and 50.6% women), ages 34.9 ± 17.8 years old, were identified. The control group consisted of 3502 age- and sex-matched subjects. The AA group was characterized by a higher blood eosinophil count (0.39 ± 0.12 cells/mm³) than the control group (0.31 ± 0.14 cells/mm³; $p < 0.001$). In the AA group, there was a higher prevalence of allergic rhinitis (odds ratio [OR] 2.15 [1.85–2.49]; $p < 0.001$), asthma (OR 1.57 [1.28–1.93]; $p < 0.001$), atopic dermatitis (AD) (OR 4.17 [3.18–5.47]; $p < 0.001$), and food allergy (OR 2.79 [1.58–4.91]; $p < 0.001$) than in the control group. The prevalence of organ-specific and systemic autoimmune diseases was significantly higher in the AA group than in the control group, with the OR of having any autoimmune disease calculated to be 4.72 (3.99–5.57; $p < 0.001$). The OR of having chronic spontaneous urticaria (CSU) with AA was 6.15 (4.06–9.32; $p < 0.001$). In patients with concomitant AA and CSU, allergic rhinitis and AD were more prevalent than in patients with CSU in the control group.

Conclusion: An estimated prevalence of AA among an Israeli population was ~0.8%. The novel finding of our study was the high prevalence of food allergy and CSU in patients with AA.

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Alopecia areata (AA) is a relatively common disease, with a global prevalence of 0.1–0.2%.^{1,2} Although the etiology of AA is still unclear, experimental and clinical evidence indicate that AA is caused by an autoimmune attack against hair follicles.³ Autoimmunity largely arises from defects in immune tolerance, which results in the production and proliferation of autoreactive T cells and autoantibodies.^{4–6} The prevalence among different ethnic groups can be higher than that observed worldwide, with an observed prevalence that ranges from ~0.7 to 3% in the United States,⁷ to ~2% in the United Kingdom.⁸

The lifetime risk of AA over 20 years was estimated to be 2.1% in Olmsted County, Minnesota.⁹ Although some epidemiologic studies reported that AA is related

to various atopic and autoimmune diseases,¹⁰ other studies calculated that the frequencies of autoimmune and atopic diseases in patients with AA are comparable with controls.¹¹ A meta-analysis of 17 studies that assessed atopic dermatitis (AD) and AA concluded that patients with AA have a significantly increased risk for AD.¹² In another study, the prevalence of AD, vitiligo, psoriasis, and lichen planus was higher in the patients with AA than in the general population.¹³ The purpose of this study was to identify clinical characteristics and the prevalence of comorbid conditions in Israeli patients with AA.

METHODS

Patients and Setting

This study was conducted by using the electronic patient record data base of the Southern Region of Leumit Health Care Services (LHS), a health maintenance organization that covers ~220,000 residents of this region of Israel. LHS has implemented an electronic patient record system that facilitates the creation of a comprehensive data base that includes the following: data on resource utilization of the covered population, demographic data, records of clinical

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visits, laboratory tests performed at a central laboratory, diagnostic codes by using the *International Classification of Diseases, Ninth Revision, Clinical Modification*,¹⁴ hospitalization, imaging and drug prescription, and purchase. This data base was mined to capture data on relevant documented diagnoses and laboratory results through cross-linking of a unique patient-identity number. This study was approved by LHS Institutional Review Committee.

All patients with an electronically documented diagnosis of AA during the years 2010–2016 were identified and were included in the AA group. The control group was composed of a random sample of the remaining LHS members, with a case-to-control ratio of two controls for each case (1:2). The randomization was performed by using the Epi Info 6 software (Atlanta, GA). Comorbidities were identified by using the *International Classification of Diseases, Ninth Revision, Clinical Modification*,¹⁴ for specific diagnostic codes registered by the board-certificated attending physicians. A patient was diagnosed with a definite rheumatic disease if he or she matched the diagnostic criteria of each specific rheumatologic disease, for example, the 1997 revised American College of Rheumatology (ACR) classification criteria for systemic lupus erythematosus,¹⁵ 1987 ACR criteria for rheumatoid arthritis,¹⁶ 2002 European criteria for Sjogren syndrome,¹⁷ 1984 modified New York criteria for ankylosing spondylitis,¹⁸ and 1980 ACR criteria for systemic sclerosis (scleroderma).¹⁹ Data capture was performed by using IBM Cognos 10.1.1 BI Report Studio software (IBM Corp., New York, NY). A chart review of all identified eligible patients was then performed to validate the cases retrieved by an electronic search. The final validated patient population was accrued and recorded into Microsoft Excel (version 14; Microsoft Corporation, Redmond, Washington) spreadsheets for analysis.

Statistical Analyses

Data were analyzed by using SPSS software version 18 (SPSS Inc., Chicago, IL). The means $\pm$ standard deviations were calculated for continuous variables. Statistical significance for categorical variables was calculated by using the χ^2 test or the Fisher exact test. The multivariate regression analyses adjusted for sex and age (odds ratio [OR] with 95% confidence intervals [CI]) were performed individually for each substratum of comorbidity to eliminate potential sources of bias. To prevent possible multiplicity issues, we applied a Bonferroni correction testing at a significance level of (0.05)/k (k - the number of independent variables/tests in Bonferroni correction) to lower the chance of a type I error. A two-tailed p value of <0.05 was considered statistically significant.

RESULTS

Demographic, Clinical, and Laboratory Characteristics of the Patients with AA and the Controls

A total of 1751 subjects, ages 34.9 ± 17.8 years old, were identified with a registered diagnosis of AA between January 1, 2010, and December 31, 2016. The study population consisted of 865 men (49.4%) and 886 women (50.6%). No differences between male and female patients were observed with respect to clinical and laboratory characteristics (Table 1). The control group consisted of 3502 age- and sex-matched subjects. The AA group was characterized by a higher blood eosinophil count (0.39 ± 0.12 cells/mm³) than the control group (0.31 ± 0.14 cells/mm³; $p < 0.001$) (Table 1).

Allergic Diseases and AA

Significant differences in the rates of allergic diseases were found between the AA and control groups. In the AA group, there was a higher prevalence of allergic rhinitis (425 [24.3%] versus 454 [12.9%] in the control group; $p < 0.001$) with OR 2.15 [95% CI, 1.85–2.49], $p < 0.001$; asthma (173 [9.9%] versus 228 [6.5%] in the control group, $p < 0.001$; with OR 1.57 [95% CI, 1.28–1.93], $p < 0.001$), AD (161 [9.2%] versus 83 [2.4%] in the control group, $p < 0.001$; with OR 4.17 [95% CI, 3.18–5.47], $p < 0.001$), and food allergy (29 [1.7%] versus 21 [0.6%] in the control group, $p < 0.001$; with OR 2.79 [95% CI, 1.58–4.91], with OR 2.79 [95% CI, 1.58–4.91], $p < 0.001$) (Table 1). No difference in the prevalence of allergic contact dermatitis was observed between the two groups.

Autoimmune Diseases and AA

Thyroid diseases were the most common autoimmune diseases associated with AA; 177 (10.1%) of the patients in the AA group had Hashimoto thyroiditis compared with 46 (1.3%) ($p < 0.001$) in the control group. The odds of having Hashimoto thyroiditis was 8.42 times greater than in the control group (6.07–11.74); $p < 0.001$ and OR of having Graves disease was 4.94 (2.78–8.67); $p < 0.001$ in the AA group compared with the control group subjects (Table 1). As presented in Table 1, the prevalence of other organ-specific and systemic autoimmune diseases was significantly higher in the AA group than in the control group, with the OR of having any autoimmune disease calculated to be 4.72 (3.99–5.57; $p < 0.001$) for the AA group compared with the control group.

Concomitant Dermatologic Diseases and AA

There were 79 cases (4.5%) of patients with chronic spontaneous urticaria (CSU) in the AA group in contrast to 32 cases (0.9%) ($p < 0.001$) of patients in the

Table 1 Demographic, clinical, and laboratory characteristics of the AA and control groups

	AA Group (n = 1751)	Control (n = 3502)	p	Multiple Logistic Regression Model OR (95% CI); p Value*
Women, no. (%)	886 (50.6)	1772 (50.6)	0.999	
Age, y	34.9 ± 17.8	35.1 ± 17.6	0.698	
Body mass index, kg/m ²	26.4 ± 3.3	26.3 ± 3.1	0.281	
White blood cell count, cells/mm ³	7.1 ± 3.7	6.9 ± 3.5	0.075	
Lymphocytes, cells/mm ³	2.4 ± 1.7	2.4 ± 1.5	0.999	
Eosinophils, cells/mm ³	0.39 ± 0.11	0.31 ± 0.14	<0.001	
Basophils, cells/mm ³	0.18 ± 0.16	0.18 ± 0.14	0.999	
Platelets cells, ×10 ⁸ /mm ³	263 ± 131	258 ± 124	0.161	
Allergic diseases, no. (%)				
Allergic rhinitis	425 (24.3)	454 (12.9)	<0.001	2.15 (1.85–2.49); <0.001
Asthma	173 (9.9)	228 (6.5)	<0.001	1.57 (1.28–1.93); <0.001
Atopic dermatitis	161 (9.2)	83 (2.4)	<0.001	4.17 (3.18–5.47); <0.001
Allergic contact dermatitis	98 (5.6)	176 (5.1)	0.392	1.12 (0.84–1.41); 0.381
Food allergy	29 (1.7)	21 (0.6)	<0.001	2.79 (1.58–4.91); <0.001
Autoimmune diseases, no. (%)				
Hashimoto thyroiditis	177 (10.1)	46 (1.3)	<0.001	8.42 (6.07–11.74); <0.001
Graves disease	41 (2.3)	17 (0.5)	<0.001	4.94 (2.78–8.67); <0.001
Type I diabetes mellitus	34 (1.9)	11 (0.3)	<0.001	6.28 (3.17–12.43); <0.001
Pernicious anemia	19 (1.1)	5 (0.1)	0.001	7.67 (2.85–20.57); <0.001
Celiac disease	36 (2.1)	19 (0.5)	<0.001	3.84 (2.20–6.72); <0.001
Inflammatory bowel disease	21 (1.2)	27 (0.8)	0.125	1.56 (0.88–2.77); 0.129
Multiple sclerosis	0	1 (0.03)	0.999	0.67 (0.02–16.36); 0.803
Sjogren disease	21 (1.2)	24 (0.7)	0.079	1.75 (0.97–3.16); 0.062
Systemic lupus erythematosus	27 (1.5)	15 (0.4)	<0.001	3.63 (1.93–6.86); <0.001
Mixed connective tissue disease	1 (0.05)	0	0.334	6.01 (0.24–147.43); 0.272
Systemic sclerosis	1 (0.05)	3 (0.09)	0.999	0.67 (0.06–6.41); 0.725
Rheumatoid arthritis	32 (1.8)	27 (0.8)	0.001	2.39 (1.43–4.01); <0.001
Overlap syndromes	11 (0.6)	10 (0.3)	0.064	2.21 (0.93–5.21); 0.071
Fibromyalgia	39 (2.2)	43 (1.2)	0.009	1.83 (1.18–2.83); 0.007
Dermatologic diseases, no. (%)				
Chronic spontaneous urticaria	79 (4.5)	32 (0.9)	<0.001	6.15 (4.06–9.32); <0.001
Psoriasis	74 (4.2)	53 (1.5)	<0.001	3.18 (2.23–4.53); <0.001
Dermatitis herpetiformis	6 (0.3)	2 (0.06)	0.021	6.01 (1.21–29.83); 0.028
Vitiligo	8 (0.4)	2 (0.06)	0.003	8.02 (1.71–37.85); 0.009
Seborrheic dermatitis	22 (1.4)	45 (1.3)	0.999	0.97 (0.58–1.63); 0.931
Rosacea	71 (4.1)	137 (3.9)	0.822	1.03 (0.77–1.39); 0.802
Erythema nodosum	3 (0.2)	4 (0.1)	0.692	1.51 (0.33–6.71); 0.595
Lichen planus	5 (0.3)	9 (0.3)	0.999	1.11 (0.37–3.32); 0.850

AA = Alopecia areata; OR = odds ratio; CI = confidence interval.

*The OR (95% CI) between the AA and control patients; a significant OR after Bonferroni correction ($p < 0.0019$; $\alpha = 0.05/27$ tests = 0.0019; $k = 27$ in Bonferroni correction).

control group. The OR of having CSU with AA was 6.15 (95% CI, 4.06–9.32; $p < 0.001$). The patients in the AA group were characterized with a higher prevalence of concomitant psoriasis (OR 3.18 [95% CI, 2.23–4.53]; $p < 0.001$) and vitiligo (OR 8.02 [1.71–37.85]; $p = 0.009$) (Table 1).

Clinical and Laboratory Characteristics of Patients with CSU with and without Concomitant AA

The subjects with CSU and with concomitant AA were more frequently women (62 [78.5%] versus 19 [59.4%] in subjects with CSU in the control group; $p =$

0.04), had higher blood levels of eosinophils (0.41 ± 0.13 cells/mm³ versus 0.28 ± 0.15 cells/mm³; $p < 0.001$) and immunoglobulin E (IgE) (175.8 ± 101.3 kU/L versus 129.5 ± 94.2 kU/L than in patients with CSU in the control group; $p = 0.028$). In patients with concomitant AA and CSU, allergic rhinitis and AD was more prevalent than in the patients with CSU in the control group (Table 2). Although there were no statistically significant differences in the prevalence of concomitant autoimmune diseases, the OR of having any concomitant autoimmune disease was 2.67 (95% CI, 1.13–6.32; $p = 0.025$) for patients with CSU from the AA group compared with the patients with CSU from the control group (Table 2).

DISCUSSION

Our study aimed to evaluate the comorbid conditions associated with AA in the Israeli population seen in the southern region of LHS during a 6-year period. There are two main findings in this study: (1) AA was associated with a higher rate of allergic diseases, such as allergic rhinitis, asthma, AD, and food allergy, and with higher blood levels of eosinophils; (2) autoimmune diseases and CSU were more prevalent in patients with AA than in sex- and age-matched controls. Indeed, many of these findings were confirmed in multiple previous studies, but the strengths of the association between AA and various comorbid conditions observed in our study were somewhat different than previously reported.

In our study, the estimated prevalence of AA among an Israeli population was ~0.8%. Our study added insight into the comorbid conditions that affect AA, and, similar to previous studies, we observed that AA was associated with allergic rhinitis, asthma, and AD.¹⁴ Previously, an important retrospective study evaluated the prevalence of comorbid conditions among 3568 patients with AA seen at tertiary care hospitals in Boston during an 11-year period and found a high prevalence of comorbid autoimmune and atopic diseases in individuals with AA.²⁰ Recently, the “Nurses’ Health Study 2” assessed the risk of AA and vitiligo associated with AD in a large cohort of U.S. women.²¹ The study found that AD was associated with an increased risk of developing AA and vitiligo in adulthood.²¹ It was intriguing that, in our study, the odds of AD in patients with AA were higher than the odds of other allergic diseases. Previously, it was indicated that concomitant AD may indicate a poor prognostic value for AA²⁰; nevertheless, our study did not include data about the AD severity and/or phenotype.

The co-occurrence of AD with AA raises the question as to whether these diseases have similar pathophysiologic mechanisms. Alternatively, shared genetics may be responsible for these associations. For example, filaggrin

gene mutations were found to be associated with more severe AA.²² There may be shared pathways that are activated in these disorders, such as type 2 T-helper (Th) deviation, Th17/Th22 cells,²³ thymic stromal lymphopoietin,²⁴ and endothelin-1.²⁵ Although AA has traditionally been considered a Th1-mediated disease, association of AA with atopic diseases^{20–22} and the proof of Th2 cytokine responses in an animal model of AA²⁶ verify the role of Th2 cells in the pathophysiology of AA. There are few studies that support a possible Th2 association of AA that have been reported lately.

Fuentes-Duculan *et al.*²⁷ studied biopsy specimens of pretreatment lesional and nonlesional scalp and of posttreatment (intralesional steroid injection) lesional scalp of six patients with patchy scalp and with AA by using immunohistochemistry and gene expression analysis. The study showed concurrent activation of both Th1 and Th2 immune axes as well as interleukin (IL) 23 and IL-32 cytokine pathways in lesional AA scalp and observed significant downregulation with corticosteroid injection in IL-12/IL-23p40, CCL18 (Chemokine [C-C motif] ligand 18), and IL-32.²¹ Suárez-Fariñas *et al.*²⁸ performed microarray and reverse transcription–polymerase chain reaction profiling of 27 lesional and 17 nonlesional scalp samples from patients with AA for comparison with 6 normal scalp samples and found that AA scalp transcriptome is associated a highly inflammatory profile of Th2, Th1, IL-23, and IL-9–Th9 pathway genes with heavy Th2 polarization, including “hallmark” atopic biomarkers.

In addition, our AA group was characterized by a higher blood eosinophil count than the control subjects. Eosinophil infiltration into the skin lesions at any stage is a valuable diagnostic element of AA.^{29,30} Previously, high serum IgE levels, eosinophilia, and infiltration of eosinophils in AA lesions were found to be correlated with AA higher severity.³¹ Another finding of our study was the higher prevalence of food allergy in patients with AA, which, to our knowledge, has not been previously described. We found only two case reports on a patient with a combination of AD, AA, and food allergy,³² and of eosinophilic esophagitis in a patient with AA.³⁰ A plausible explanation for this finding was that eosinophils express chemokine receptors, such as CCR3 (C-C chemokine receptor type 3) and CCR4 (Chemoattractant receptor-homologous molecule expressed on Th2 cells), and, in Th2-predominant inflammation, their recruitment and accumulation may occur *via* stimulation of these receptors.³³

Our results were consistent with the previous findings of an increased prevalence of several systemic and organ-specific autoimmune diseases in patients with AA.^{20–22} As in previous studies, the main association for AA in our cohort was thyroid autoimmunity.³⁴ Recently, diabetes mellitus (both types) was found in 11.1% of patients with AA²⁰; we also observed an in-

Table 2 CSU severity and responses to treatment in the patients with CSU and with and without AA

	CSU with AA (n = 79)	CSU without AA (n = 32)	p
Women, no. (%)	62 (78.5)	19 (59.4)	0.040
Age, mean $\pm$ SD, y	32.7 $\pm$ 14.2	34.1 $\pm$ 16.5	0.654
Body mass index, mean $\pm$ SD, kg/m ²	26.2 $\pm$ 3.1	26.4 $\pm$ 3.2	0.761
Angioedema, no. (%)	24 (30.4)	7 (21.8)	0.365
ASST, performed/positive result (%)	53/28 (52.8)	19/7 (36.8)	0.231
Eosinophils, mean $\pm$ SD, no. cells/mm ³	0.41 $\pm$ 0.13	0.28 $\pm$ 0.15	<0.001
Basophils, mean $\pm$ SD, no. cells/mm ³	0.12 $\pm$ 0.09	0.13 $\pm$ 0.11	0.621
Anti-TPO ab test, performed/positive result (%)	61/24 (39.3)	26/7 (26.9)	0.268
Antithyroglobulin ab, no. performed/positive results (%)	61/10 (16.4)	26/4 (15.4)	0.906
ANA, performed/positive (%)	73/7 (9.6)	28/2 (7.1)	0.497
hs-C reactive protein value, mean $\pm$ SD, mg/L	7.4 $\pm$ 9.1	5.7 $\pm$ 8.4	0.364
TSH value, mean $\pm$ SD, uIU/mL	2.5 $\pm$ 1.7	2.3 $\pm$ 1.4	0.557
Serum IgE level, mean $\pm$ SD, kU/L	175.8 $\pm$ 101.3	129.5 $\pm$ 94.2	0.028
25-Hydroxyvitamin D, mean $\pm$ SD, nmol/L	22.3 $\pm$ 11.5	23.1 $\pm$ 12.1	0.744
Allergic diseases, no. (%)			
Allergic rhinitis	29 (36.7)	5 (15.6)	0.029
Asthma	8 (10.1)	2 (6.2)	0.721
Atopic dermatitis	15 (18.9)	1 (3.1)	0.028
Allergic contact dermatitis	5 (6.3)	2 (6.2)	0.962
Food allergy	1 (1.3)	0	0.522
Autoimmune diseases, no. (%)			
Hashimoto thyroiditis	23 (29.1)	4 (12.5)	0.055
Graves disease	2 (2.5)	0	0.363
Type I diabetes mellitus	2 (2.5)	0	0.363
Pernicious anemia	1 (1.3)	0	0.522
Celiac disease	3 (3.8)	1 (3.1)	0.863
Inflammatory bowel disease	1 (1.3)	1 (3.1)	0.504
Multiple sclerosis	0	0	0.999
Sjogren disease	4 (5.1)	1 (3.1)	0.655
Systemic lupus erythematosus	3 (3.8)	1 (3.1)	0.863
Mixed connective tissue disease	0	0	0.999
Systemic sclerosis	0	0	0.999
Rheumatoid arthritis	2 (2.5)	0	0.363
Overlap syndromes	1 (1.3)	0	0.522
Fibromyalgia	3 (3.8)	2 (6.2)	0.572
Dermatologic diseases, no. (%)			
Psoriasis	4 (5.1)	1 (3.1)	0.655
Dermatitis herpetiformis	0	0	0.999
Vitiligo	2 (2.5)	0	0.363
Seborrheic dermatitis	1 (1.3)	1 (3.1)	0.504
Rosacea	3 (3.8)	2 (6.2)	0.572
Erythema nodosum	0	0	0.999
Lichen planus	0	0	0.999

CSU = Chronic spontaneous urticaria; AA = alopecia areata; SD = standard deviation; ASST = autologous serum skin test; TPO = thyroid peroxidase; ab = antibody; ANA = antinuclear antibody; hs-C reactive protein = a high-sensitivity C-reactive protein; TSH = thyroid-stimulating hormone; IgE = immunoglobulin E; uIU/mL = microgram international units per milliliter.

Anti-TPO ab (anti-thyroid peroxidase antibodies) >75 IU/mL and/or antithyroglobulin (ab) antibodies >150 IU/mL.

creased prevalence of IDDM (Insulin-Dependent Diabetes Mellitus) in patients with AA and with an OR of 6.28 compared with controls; however, the novel finding of our study was the high prevalence of CSU in patients with AA that has not been reported. Several mechanisms have been investigated as possibly contributing to the pathogenesis of CSU, including autoimmunity.³⁵ The autologous serum skin test (ASST) is considered to be a screening test for autoimmune CSU because of IgG–anti-IgE autoantibodies, anti-FcεRI (high-affinity IgE receptor, [or Fc epsilon RI]) autoantibodies, or both.³⁶

A negative ASST result has a high predictive value for the absence of circulating functional autoantibodies, therefore, to assess the rate of possible autoimmunity in CSU, we compared the ASST positivity in the patients with concomitant AA and CSU, and in those with CSU from the control group. Rates of ASST positivity were similar in patients with CSU and with and without AA. Recently, autoreactive CD4⁺ T cells that target FcεRIα were detected in most subjects with CSU, with a cytokine secretion profile typical of a Th1 cell response.³⁷ However, in biopsy specimens of CSU wheals, Th2 and Th17 cells were significantly more frequent than in controls.³⁸ Recently, we observed an association between CSU and atopic diseases.³⁹ It is noteworthy that AD is also accompanied by expansion of skin-homing Th2 and Th22 subsets with lower Th1 frequencies.⁴⁰ The presence of atopic diseases is significantly associated with risks of autoimmune diseases, and the coexistence of AD, allergic rhinitis, and asthma exacerbates the risk of autoimmunity.⁴¹

Evidence that supports a genetic basis of autoimmunity for AA originates from multiple lines of epidemiologic and genetic studies.⁴² The first genome-wide association study of AA involved a total of 1054 cases of patients with AA (U.S. patients of self-reported European ancestry) and 3278 controls, and investigated genome-wide significance for most genomic regions implicated in autoimmunity and in T-cell-mediated pathways.³⁶ The study defined the genetic underpinnings of AA, which placed it within the context of shared pathways among autoimmune diseases, revealed the upregulation of ULBP (UL16-binding proteins) ligands in triggering autoimmunity.⁴³ In a follow-up study, a genome-wide significant association was found for IL-13 and KIAA0350/CLEC16A (C-type lectin domain family 16, member A) as susceptibility loci for AA, whereas IL-13 and KIAA0350/CLEC16A are also susceptibility loci for other autoimmune diseases, which supports the hypothesis of shared pathways of autoimmune susceptibility.⁴⁴

CONCLUSION

Our results, together with epidemiologic links between AA and atopy and robust genetic associations of

an IL-13 pathway with AA further supported a feasible pathogenic role of the Th2 axis in the pathophysiology of AA. Therefore, there is a rationale for investigating Th2-targeting strategies for patients with AA because Th2-targeting strategy was found to be effective in AD and asthma.^{45,46} The link of AA and CSU may also indicate that targeting FcεRIα on mast cells and IgE might also provide possible benefit in patients with AA. Recent reports that antihistamines may be beneficial in at least some patients with AA emphasize the practical clinical relevance of targeting mast cells in AA.^{47,48} We suggest that more specific therapies should be considered, including the use of bispecific antibodies so as to selectively block mast cells.

The strengths of our study were that our team used the electronically documented AA registry and then manually ensured that relevant data were obtained for all the patients. The main limitation of this study was that, as a retrospective study, it may have information bias because of possible inaccurate clinical records, loss to follow-up, and missing data. Future prospective studies should be aimed at closing the gaps of knowledge on the role of atopy and autoimmunity in patients with CSU and AA.

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