

Clinical-laboratory characteristics of ANA-positive chronic idiopathic urticaria

Eli Magen, M.D.,^{1,2} Dan-Andrei Waitman, M.D., M.P.H.,¹ Yoav Dickstein, Ph.D.,¹
Valentina Davidovich, M.Sc.,¹ Natan R. Kahan, Ph.D., M.H.A.^{1,3}

ABSTRACT

Despite the established association between chronic idiopathic/spontaneous urticaria (CIU) and presence of antinuclear antibodies (ANAs), the prevalence of autoimmune comorbidities in this population has not been analyzed. Here, we aim to identify clinical and laboratory manifestations associated with ANA-positive CIU. ANA-positive patients were identified via electronic data capture from the electronic patient record database of Leumit Health care Services (LHS) of Israel. Patient characteristics, medical histories, and details of diagnostic workup, medical treatment, and follow-up were retrieved by performing a chart review of electronic patient records (EPRs). The prevalence of target diseases among ANA⁺ CIU⁺, ANA⁺ CIU⁻, and ANA⁻ CIU⁺ patients was calculated. A total of 91 ANA⁺ CIU⁺, 3131 ANA⁺ CIU⁻, and 478 ANA⁻ CIU⁺ patients were identified. The ANA⁺ CIU⁺ group was characterized by higher prevalence of Sjögren's syndrome (SS)-A 52 antibodies (Ab) (7.7% versus 2.4%; $p = 0.008$), SS-A 60 Ab (11% versus 2.8%; $p < 0.001$), and SS-B Ab (14.3% versus 3.2%; $p < 0.001$), compared with ANA⁻ CIU⁺ group. Additionally, ANA⁺ CIU⁺ patients were more likely to be diagnosed with thyroid autoimmune diseases, higher C-reactive protein (6.4 ± 10.3 versus 4.1 ± 8.8 mg/L; $p = 0.027$), and more profound basopenia (0.04 ± 0.09 versus 0.15 ± 0.11 cell/mm³; $p < 0.001$) than ANA⁻ CIU⁺ patients. More ANA⁺ CIU⁺ patients were resistant to four-fold standard licensed doses of antihistamines than ANA⁻ CIU⁺ patients [11 (12.1%) versus 29 (6.1%); $p = 0.046$]. ANA-positive CIU is characterized by higher prevalence of SS-A 52, SS-A 60, and SS-B antibodies and poorer clinical response to antihistamine medications.

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It is estimated that urticaria will affect 20%–25% of the population at some point in their lifetime.¹ Chronic urticaria (CU) involves hives that typically present for durations more than six weeks. Although CU generally lasts one to five years, prolonged cases lasting up to five years occur in approximately 14% of patients.² Chronic idiopathic/spontaneous urticaria (CIU) has no discernable external cause.³ Autoimmune CU (AIU) is implicated as a principal cause of CIU, potentially explaining 30%–50% of previously idiopathic cases.⁴ In AIU, the involvement of pathogenic autoantibodies causing release of histamine after reaction with immunoglobulin E (IgE) epitopes, or with the α -chain of the high-affinity receptor for IgE (Fc ϵ RI) receptors, should be considered,^{5,6} whereas the presence of these autoantibodies has been found to be related with exacerbation of the disease.⁷ It is well accepted that the autoimmune mechanisms could be detected in AIU patients by the autologous serum skin test (ASST) and by immunoassay.^{4–9} Due to the recog-

nized correlation between the presence of anti-Fc ϵ RI and anti-IgE autoantibodies and positive ASST, in clinical practice, the positive ASST is generally suggestive of the autoimmune pathogenesis of CIU.^{10,11}

Thyroid disease is the most commonly reported autoimmune condition in patients with CIU. Published studies have reported frequencies of thyroid autoimmunity in patients with CIU ranging from 23% to 39%; moreover, antithyroid antibodies do have increased incidence in those with antibody to the IgE receptor.¹² Patients with coexistent thyroid autoimmunity and CIU have a more severe and prolonged course of urticaria than those without thyroid autoimmunity.¹³ In addition to thyroid disease, possible associations between other autoimmune diseases and CIU have been evaluated. Confino-Cohen *et al.* found that 12.5% of patients had one additional autoimmune disease, 2.1% had two diseases, 0.1% had three diseases, and single patients each had additional four or five diseases.¹⁴

Antinuclear antibodies (ANAs) are a group of autoantibodies directed against corresponding antigens in the nucleus and are found in many patients with systemic or organ-specific autoimmune disorders.¹⁵ The percentage of CIU patients having a positive test for ANAs (titer more than 1:160) is approximately 29%.¹⁶ The detection of ANA in serum has been performed for many years to screen for autoimmune diseases. Indirect immunofluorescence assay is considered the gold

¹Leumit Health Services, Israel, ²Clinical Immunology and Allergy Unit, Barzilai Medical Center, Ben Gurion University of the Negev, Israel, and ³School of Public Health, Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel
The authors have no conflicts of interest to declare pertaining to this article
Address correspondence to Eli Magen, M.D., Clinical Immunology and Allergy Unit, Ben Gurion University of Negev, Barzilai University Medical Center, Ashkelon, Israel
E-mail address: allergologycom@gmail.com

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standard. However, immunofluorescence assay for ANA screening is subjective, labor intensive, and has an imprecise end point and yields a significant number of false-positive results among asymptomatic controls.¹⁷ The recently developed multiplex ANA assay simultaneously measures multiple specific ANAs using bead technology (Luminex, Austin, TX).^{18,19}

To the best of our knowledge, there are no published studies investigating the clinical and laboratory features of ANA-positive CIU according to the ANA profile. Although it may be important to recognize the presence of these autoimmune biomarkers to understand the mechanism of CIU, it may be beneficial to investigate any clinical relevance or associations these autoimmune biomarkers may have to the clinical characteristics of the disease. The purpose of this study was to identify clinical and laboratory patient attributes associated with ANA-positive CIU according to multiplex ANA assay markers.

MATERIALS AND METHODS

Patients and Setting

This study was conducted using the electronic patient record (EPR) database of Leumit Health care Services (LHS), a health maintenance organization that covers approximately 720,000 residents of Israel nationwide. LHS has implemented an EPR system that facilitates a database that includes comprehensive information on the insured population and resource utilization, such as demographic data, records of clinical visits, laboratory tests performed at a single centralized laboratory, and diagnostic codes using the International Classification of Diseases, 9th Revision, Clinical Modification. This database was used to obtain information on diagnoses and laboratory results by means of cross-linking data using a unique patient identifier. Data capture was performed using IBM Cognos 10.1.1 BI Report Studio software. Results of queries were downloaded into Microsoft Excel (version 14) spreadsheets for analysis. This study was approved by the Asaf-haRofe Medical Center and LHS Institutional Review Committee.

All patients with an electronically documented diagnosis of CIU during the year 2012 were included in the study, whereas the patients with a recorded diagnosis of other forms of urticaria were excluded. All cases with ANA-positive CIU were included in the ANA⁺ CIU⁺ group, whereas the remaining ANA-positive subjects without CIU were included in the ANA⁺ CIU⁻ group. Additionally, we retrospectively reviewed the computerized database from our allergy/clinical immunology unit for the period January 1, 2012, through December 31, 2012, to identify patients with ANA⁻ CIU (ANA⁻ CIU⁺ group). Patient characteristics, medical histories, and details of diagnostic

workup, medical treatment, and follow-up were retrieved by performing a chart review of EPRs. Detailed analysis of antihistamine medication usage was also performed.

Comorbidities were identified by specific International Classification of Diseases, 9th Revision, Clinical Modification diagnostic codes registered by the attending board-certified physicians. Every patient with positive ANA was examined for the symptoms and signs of rheumatic diseases. A patient was diagnosed with a definite rheumatic disease if he or she matched the diagnostic criteria of each specific rheumatological disease. For example, the 1997 revised American College of Rheumatology (ACR) classification criteria for systemic lupus erythematosus (SLE), 1987 ACR criteria for rheumatoid arthritis (RA), 2002 European criteria for Sjögren's syndrome (SS), 1984 modified New York criteria for ankylosing spondylitis, and 1980 ACR criteria for systemic sclerosis (Scleroderma).

Laboratory Workup

LHS's central laboratory uses the BioPlex 2200 ANA screen (by Bio-Rad; Bio-Rad Laboratories, Hercules, CA), which is a fully automated Luminex-based system developed for high-throughput analysis of 13 autoimmune analytes simultaneously in a single tube. This system allows the simultaneous detection in one sample of 13 autoantibodies [reacting with SSA (52 and 60 kDa), SSB, anti-Smith, anti-Smith/ribonucleoprotein (RNP), RNP-A, RNP-68 kDa, scleroderma 70, centromere B, double-stranded DNA (ds-DNA) antibodies, chromatin, histidyl t-RNA synthetase, and ribosomal P proteins]. ANA screen is reported positive if any of the 13 autoantibodies investigated is positive (above cut-off level), and this report shows the actual levels of individual analytes. For clinical-laboratory workup, all CIU patients at LHS are routinely screened for the presence of antithyroglobulin, antitopoisomerase antibodies, rheumatoid factor (RF), complement component 3 + complement component 4 and thyroid-stimulating hormone levels, erythrocyte sedimentation rate, C-reactive protein, complete blood count, and liver enzymes.

Statistical Analyses

Data was analyzed using SPSS Software version 18 (SPSS Inc., IBM-SPSS, Chicago, IL). The mean and standard deviation were calculated for continuous variables. Statistical significance for categorical variables was calculated using χ^2 test or Fisher's exact. Two-tailed $p < 0.05$ was considered statistically significant.

RESULTS

We identified 22,266 patients that performed an ANA test between January 1 and December 31, 2012. The predominant reason for measurement of ANA was presence

Table 1 Clinical and laboratory characteristics ANA-positive subjects with and without CIU

	ANA ⁺ CIU ⁺ Group N = 91	ANA ⁺ CIU ⁻ Group N = 3131	p Value
Age (years)	46.9 ± 18.2	43.2 ± 21.7	0.108
Sex (male) (n/%)	16 (17.6%)	748 (23.9%)	0.210
Rheumatoid factor	15 (16.5%)	506 (16.2%)	0.885
Anti-DNA titre	8.1 ± 14.3	10.3 ± 16.5	0.208
Anti-DNA (n/%)	9 (9.9%)	338 (10.8%)	1
SS-A 52 Ab (n/%)	7 (7.7%)	76 (2.4%)	0.008
SS-A 60 Ab (n/%)	10 (11%)	87 (2.8%)	<0.001
SS-B Ab (n/%)	13 (14.3%)	101 (3.2%)	<0.001
Jo-1 Ab (n/%)	1 (1.1%)	38 (1.2%)	1
Centromere B Ab (n/%)	0	7 (0.2%)	1
Chromatin Ab (n/%)	2 (2.2%)	52 (1.7%)	0.668
Ribosomal P Ab (n/%)	1 (1.1%)	42 (1.3%)	1
RNP 68 Ab (n/%)	3 (3.3%)	116 (3.7%)	1
RNP A Ab (n/%)	32 (35.2%)	1075 (34.3%)	0.911
Scl-70 Ab (n/%)	5 (5.5%)	87 (2.8%)	0.186
Smith (Sm) Ab (n/%)	4 (4.4%)	147 (4.7%)	1
SmRNP Ab (n/%)	5 (5.5%)	182 (5.8%)	1
Graves' disease (n/%)	5 (5.5%)	34 (1.1%)	0.004
Hashimoto's thyroiditis (n/%)	21 (23.1%)	166 (5.3%)	<0.001
Connective tissue diseases	15 (16.5%)	594 (18.9%)	0.783
Systemic lupus erythematosus	4 (4.4%)	314 (10%)	0.076
Sjögren's syndrome	3 (3.3%)	109 (3.4%)	1
Rheumatoid arthritis	2 (2.2%)	85 (2.7%)	1
Ankylosing spondylitis	1 (1.1%)	18 (0.6%)	0.102
Systemic sclerosis	2 (2.2%)	15 (0.5%)	0.094
Polymyositis/dermatomyositis	0	7 (0.2%)	1
Mixed connective tissue disease	0	14 (0.4%)	1
Overlap syndromes	3 (3.3%)	32 (1.2%)	0.075

Overlap syndromes, at least two connective tissue diseases, include systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, polymyositis/dermatomyositis, and Sjögren's syndrome.

CIU = chronic idiopathic urticaria; Sm = anti-Smith antibodies; Scl-70 = scleroderma 70; Jo-1 = histidyl t-RNA synthetase.

of autoimmunity-related symptoms. A positive ANA result was recorded for 3222 of these patients (14.5%). A total of 91 subjects with a mean age of 46.9 ± 18.2 years were diagnosed CIU and tested positive for ANA, whereas 3131 subjects with a mean age of 43.2 ± 21.7 years tested positive for ANA without a registered diagnosis of CIU. ANA⁺ CIU⁺ group was characterized by higher frequency of SS-A 52 antibodies (Ab) [7 (7.7%) versus 76 (2.4%); $p = 0.008$], SS-A 60 Ab [10 (11%) versus 87 (2.8%); $p < 0.001$], and SS-B Ab [13 (14.3%) versus 101 (3.2%); $p < 0.001$] than ANA⁺ CIU⁻ group. There were no differences between the two groups in the demographic and other laboratory characteristics (Table 1). From the accompanying autoimmune disorders, there was higher frequency of Graves' disease [5 (5.5%) versus 34 (1.1%); $p = 0.004$] and Hashimoto's thyroiditis [21 (23.1%) versus 166 (5.3%); $p < 0.001$] in ANA⁺ CIU⁺ group (Table 1). ANA⁺ CIU⁺ group was characterized by an increased higher incidence of antithyroid antibodies

than ANA⁻ CIU⁺ group; and in both groups, antitopoisomerase antibodies had a higher incidence than antithyroglobulin antibodies (Table 2). ANA⁻ CIU⁺ group included 478 subjects aged 43.81 ± 17.27 years. ANA⁺ CIU⁺ group was characterized with higher prevalence of thyroid autoimmune and connective tissue diseases (Table 2), mild elevation of C-reactive protein (6.4 ± 10.3 versus 4.1 ± 8.8 mg/L; $p = 0.027$), and more profound basopenia (0.04 ± 0.09 versus 0.15 ± 0.11 cell/mm³; $p < 0.001$) than ANA⁻ CIU⁺ group. There was no difference in urticaria activity score (UAS) at presentation between ANA⁺ CIU⁺ and ANA⁻ CIU⁺ groups. Treatment with standard licensed doses of antihistamines was less effective in ANA⁺ CIU⁺ than in ANA⁻ CIU⁺ group [45 (49.5%) versus 295 (61.7%); $p = 0.035$]. More subjects were resistant to four-fold standard licensed doses of antihistamines in ANA⁺ CIU⁺ than in ANA⁻ CIU⁺ group [11 (12.1%) versus 29 (6.1%); $p = 0.046$].

Table 2 Clinical and laboratory characteristics CIU subjects with positive and negative ANA

	ANA ⁺ CIU ⁺ Group N = 91	ANA ⁻ CIU ⁺ Group N = 478	p Value
Age (years)	46.85 ± 18.19	43.81 ± 17.27	0.128
Sex (male) (n/%)	16 (17.6%)	109 (22.7%)	0.336
Angioedema	27 (29.7%)	114 (23.8%)	0.235
Concomitant dermatographism/DU	24 (27.7%)	96 (20.1%)	0.206
Basophils (cell/mm ³)	0.04 ± 0.09	0.15 ± 0.11	<0.001
IgE (U/mL)	185.5 ± 346.6	126.4 ± 309.8	0.102
Thyroglobulin Ab (n/%)	19 (20.9%)	334 (10.4%)	<0.001
TPO Ab (n/%)	25 (27.5%)	394 (12.2%)	<0.001
T3	1.9 ± 0.9	1.8 ± 0.9	0.331
T4 (9–19 pmol/L)	14.3 ± 2.6	14.7 ± 2.9	0.221
TSH (0.35–4.94 mIU/L)	2.2 ± 1.6	2.3 ± 1.8	0.621
25-hydroxyvitamin D (nmol/L)	21.8 ± 10.2	23.6 ± 12.1	0.184
C4 (g/L)	36.1 ± 18.7	34.7 ± 19.4	0.525
C3 (g/L)	120.9 ± 23.8	116.9 ± 25.3	0.163
ESR (mm/h)	21.2 ± 18.9	19.7 ± 15.4	1
C-reactive protein (mg/L)	6.4 ± 10.3	4.1 ± 8.8	0.027
Pernicious anemia/B12 deficiency	4 (4.4%)	27 (0.6%)	0.803
Autoimmune hepatitis	1 (1.1%)	0	0.159
Primary biliary cirrhosis	1 (1.1%)	0	0.159
Celiac disease	3 (3.3%)	21 (0.4%)	1
IDDM	1 (1.1%)	0	0.159
Graves' disease (n/%)	5 (5.5%)	8 (1.7%)	0.042
Hashimoto's thyroiditis (n/%)	21 (23.1%)	68 (14.2%)	0.040
Connective tissue diseases	15 (16.5%)	5 (1%)	<0.001
Systemic lupus erythematosus	4 (4.4%)	0	<0.001
Sjögren's syndrome	3 (3.3%)	0	0.004
Rheumatoid arthritis	2 (2.2%)	3 (0.6%)	0.182
Ankylosing spondylitis	1 (1.1%)	2 (0.4%)	0.406
Systemic sclerosis	2 (2.2%)	0	0.025
Polymyositis/dermatomyositis	0	0	1
Mixed connective tissue disease	0	0	1
Overlap syndromes	3 (3.3%)	0	0.004

Anti-TPO antibodies more than 75 IU/mL and/or antithyroglobulin antibodies more than 150 IU/mL.

CIU = chronic idiopathic urticaria; DU = dermatographic urticaria; ESR = erythrocyte sedimentation rate; TPO = thyroid peroxidase; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; C3 = complement component 3; C4 = complement component 4; ESR = erythrocyte sedimentation rate.

DISCUSSION

This study presents the clinical and laboratory features of 91 patients with ANA-positive CIU. There are four main findings of this study: 1) ANA⁺ CIU⁺ is associated with a higher prevalence of thyroid autoimmunity rheumatic diseases; 2) SS-A 52 Ab, SS-A 60 Ab and SS-B Ab are more prevalent in ANA⁺ CIU⁺ than in ANA⁺ CIU⁻; 3) ANA⁺ CIU⁺ is characterized with more profound basopenia than ANA⁻ CIU⁺; and 4) ANA⁺ CIU⁺ is characterized by less responsiveness to the treatment with standard licensed doses of antihistamines and more antihistamine resistance.

ANAs are detectable in approximately 5%–25% and are significantly elevated in approximately 2.5% of the

population, whereas most individuals with a positive ANA do not have an autoimmune disease.²⁰ This is consistent with the finding that the prevalence of all autoimmune disorders is 5%–7%.²¹ Therefore, ANA positivity in the human population suggests that ANAs may be an important component of the usual immune activation. Consequently, most of the consultations for ANA positivity seen in rheumatology clinics are not associated with any identifiable disease.

CIU is associated with autoreactivity/autoimmunity in at least one-third of patients, and details of the autoimmune pathogenesis of CIU have been reviewed elsewhere.³ In our setting, positive ANA is observed in 10%–14% of CIU patients,²² which is quite comparable

Table 3 CIU severity and responses to treatment in CIU subjects with positive and negative ANA

	ANA ⁺ CIU ⁺ Group N = 91	ANA ⁻ CIU ⁺ Group N = 478	p Value
UAS at presentation	3.8 ± 0.9	3.7 ± 0.7	0.235
Fexofenadine 180 mg/d (n/%)	68 (74.7%)	339 (70.9%)	0.527
Cetirizine 10 mg/d (n/%)	11 (12.1%)	71 (14.9%)	0.625
Desloratadine 5 mg/d (n/%)	4 (4.4%)	23 (4.8%)	1
Loratadine 10 mg/d (n/%)	8 (8.8%)	45 (9.4%)	1
Complete freedom from symptoms with standard licensed dose of antihistamine after two months (n/%)	45 (49.5%)	295 (61.7%)	0.035
Changes from one antihistamine to another (n/%)	8 (8.8%)	34 (7.1%)	0.518
Adding of first generation antihistamine (n/%)	5 (5.5%)	16 (3.4%)	0.357
Up-dosing with H1-antihistamines (n/%)	42 (46.1%)	157 (32.8%)	0.016
Antihistamine resistant CIU (n/%)	11 (12.1%)	29 (6.1%)	0.046

with that observed in other studies.^{14,16,23} The higher prevalence among female patients in our study population was similar to that in other epidemiologic surveys of CIU.²⁴ Although measuring ANA serves as a nonspecific marker of systemic autoimmunity in rheumatologic disorders, its relationship with CIU is poorly understood. Nonetheless, positive ANA has been found to have some correlation with CIU severity and was strongly associated with refractoriness to antihistamines.¹⁶ In this study, we also evaluated the possible correlation of ANA positivity with CIU severity and responses to treatment (Table 3). According to the EPR at the first visits, there was no difference in UAS between ANA⁺ CIU⁺ and ANA⁻ CIU⁺ groups. Because this was a retrospective study, evaluation of ANA⁺ CIU⁺ severity using the UAS7 (UAS over one week) was not feasible, limiting our ability to discuss levels of CIU severity in this patient population. Nevertheless, the clinical response to antihistamine medications was more favorable in ANA⁻ CIU⁺ group, whereas more antihistamine refractory cases were observed in ANA⁻ CIU⁺ group substantiating previous observation published by Viswanathan *et al.*¹⁶

In the ANA⁺ CIU⁺ group, the prevalence of anti-SSA and anti-SSB antibodies was 17.7% and 14.3%, respectively and was higher than ANA⁺ CIU⁻ subjects. Anti-SSA and anti-SSB antibodies are among the most commonly identified autoantibodies in the routine screening for systemic autoimmune diseases, and the presence of these antibodies may generally implicate underlying rheumatic diseases in the affected population. However, in our study, no difference in the prevalence of rheumatic diseases was observed between the ANA⁺ CIU⁺ and ANA⁺ CIU⁻ groups. On the other hand, ANA⁺ CIU⁺ patients were characterized by higher prevalence of rheumatic diseases than

those in the ANA⁻ CIU⁺ group. Anti-SSA/SSB autoantibodies are characteristic of SS and may be involved in its pathogenesis.^{25,26} Nearly half of the patients with SS develop cutaneous manifestations, which may include xeroderma, purpura, and/or urticaria-like lesions.²⁷ However, these autoantibodies are also prevalent in many autoimmune diseases and are neither specific to SS nor correlated with its clinical severity.²⁸ In most cases, anti-SSA/SSB antibodies appear many years before clinical onset of SS.²⁹ Therefore, we cannot exclude the possibility that SS-A 52 Ab, SS-A 60 Ab, and SS-B Ab-seropositive CIU patients may have had undiagnosed SS or may develop the disease in their future. However, the significance of these antibodies for determining prognosis and treatment in CIU remains to be determined in prospective investigations. Due to retrospective nature of our study, we cannot say whether our anti-SSA/SSB-positive CIU patients have undiagnosed SS.

Although anti-SSA/SSB antibodies can be detected in 70%–100% of patients with SS, they are also detectable in sera of approximately 30% patients with SLE and in 5%–20% of patients with discoid lupus erythematosus.³⁰ Moreover, anti-SSA antibodies can be found earlier than other SLE-related autoantibodies and are present on average 6.6 years before the diagnosis of SLE.³¹ Notably, only 4.4% of our ANA-positive CIU patients were diagnosed with SLE. Other ANA-positive CIU patients do not fulfil the ACR criteria to diagnose SLE. Systemic lupus erythematosus is not infrequently associated with urticarial lesions, generally fulfilling the criteria of urticarial vasculitis and usually arising during the active stage of the disease.³¹ There are no published prospective studies to identify CIU as the presenting manifestation of SLE. Nevertheless, in the study of Confino-Cohen *et al.*, most patients

were diagnosed with an additional autoimmune disease in the 10 years after the CIU diagnosis.¹⁴

In addition, although the prevalence of positive anti-ds-DNA in ANA⁺ CIU⁺ group was 9.9%, actually, without concomitant SLE and overlap syndromes, the prevalence of anti-ds-DNA was 2.4%. Theoretically, some of ANA⁺ CIU⁺ patients might have undiagnosed SLE, because anti-ds-DNA can be positive for years before clinical symptoms of SLE develop.³²

The presence of antithyroid antibodies in CIU clearly correlates with the presence of antibodies to FcεRI (or to IgE), although there is not an absolute concordance between them.³³ Our study confirms the relationship between CIU and thyroid autoimmunity as suggested in the previous works.^{14,34} ANA positivity has previously been reported to be approximately 7.9% in CIU patients with thyroid autoimmunity.³⁵ Autoimmune thyroid diseases are much more common than systemic rheumatological diseases, and a significant proportion of the asymptomatic ANA positivity seen by rheumatologists is related to thyroid autoimmunity.³⁶

Several studies have shown peripheral blood basopenia in patients with CIU.^{37,38} Moreover, basopenia is inversely related to the severity of CIU.³⁹ Our ANA⁺ CIU⁺ patients were characterized with profound basopenia. Such patients have previously been characterized by the high levels of autoantibodies.⁴⁰ Basophils from patients with systemic rheumatological diseases respond to anti-DNA and ANAs with histamine release, and this response was well correlated to the clinical activity of these diseases.⁴¹ Moreover, in patients with RA, IgE-anticitrullinated protein antibody can bind to FcεRI on basophils and can directly activate basophils of anticitrullinated protein antibody⁺ RA patients.⁴² Whether similar mechanisms are relevant in pathophysiology of CIU have to be addressed in further studies.

This study has several limitations due to the retrospective design implemented. The prevalence of some diseases in ANA⁺ CIU⁻ group may be underestimated because only symptomatic patients were screened for ANA.

Additionally, we did not perform immunoassays for the presence anti-FcεRI and anti-IgE autoantibodies and basophil studies, which can better identify a subpopulation of CIU patients with AIU.⁴³ Because laboratory testing may be justified based on its "reassurance value," extensive routine testing in CIU is not favorable from a cost-benefit standpoint and does not lead to improved patient care outcomes.⁴⁴

To further validate our findings and to better characterize clinical and pathophysiological features of ANA⁺ CIU⁺ subjects, prospective studies are needed. Additionally, objective documentation of CIU severity is necessary to accurately assess effectiveness of therapies over long periods of time.⁴⁵ Principal features of

any future investigation would be 1) an assessment of all autoimmune biomarkers and ASST at an initial visit; 2) evaluation of disease severity using a validated protocol such as the UAS7; 3) an assessment of clinical response to antihistamine medications as refractory or controlled; 4) histologic features of urticarial wheals in ANA⁺ versus ANA⁻ CIU; and 5) to better clarify the real role of infectious agents in the pathogenesis of autoimmunity and their relative prevalence CIU.⁴⁶

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