A retrospective review of clinical presentation, thyroid autoimmunity, laboratory characteristics, and therapies used in patients with chronic idiopathic urticaria

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Background: Our knowledge of autoimmune characteristics of chronic idiopathic urticaria (CIU) is limited.

Objective: To study the demographic, laboratory, and clinical patterns of a cohort of patients with CIU.

Methods: We evaluated 236 patients with CIU seen in a recent 2-year span. For serum basophil activation testing (BAT-CD203), the samples were sent to the National Jewish Medical and Research Center for donor basophil CD203 expression assay (5% cell surface expression was considered a positive result).

Results: Of the 236 patients with CIU, 77% were females with a mean age of 39 years. The mean age of males was 43 years. Of patients tested for BAT-CD203 (50 females and 8 males), 38% of females (n = 19) and 13% of males (n = 1) had positive test results. Of the 146 females and 42 males tested for thyroid autoimmunity (TA), 34% of females (n = 50) and 17% of males (n = 7) had underlying TA. Nine BAT-CD203–positive females (47%) had TA compared with 11 of 30 BAT-CD203–negative females (37%). No correlation was found between antinuclear antibodies and BAT-CD203. Cyclosporine or corticosteroids were used in 28% of the study population, with another 16% requiring a trial of additional third-line agents with or without prednisone/cyclosporine. There was no significant difference in the maximum number of medications used in subgroups based on the presence or absence of BAT-CD203 and TA.

Conclusions: The frequency of TA in patients with CIU was 30%, which is higher than that previously reported. The frequency of TA and BAT-CD203 positivity was higher in females. In this clinical cohort, there was no correlation between BAT-CD203 and TA.

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INTRODUCTION

Urticaria is a common dermatologic condition that affects 15% to 25% of the population at some point in life.[1] Chronic urticaria (CU) is defined as the occurrence of continuous, or intermittent, hives for at least 6 weeks. The lesions are typically edematous pink or red wheals of variable size and shape, with surrounding erythema, and are generally pruritic. Chronic idiopathic urticaria (CIU) constitutes 80% to 90% of patients with CU[1] and affects up to 0.5% to 5% of the population at some time in life.[2–4] Up to 20% of patients with CIU can have symptoms for longer than 10 years. CIU is more common in adults than in children. There is a female to male ratio as high as 4:1, with the highest incidence in middle-aged women. Almost 50% of patients with urticaria present with associated angioedema, whereas 40% have urticaria alone and 10% have isolated angioedema without urticaria.[1] It has been reported that CIU is a major affliction that causes serious disability to a degree equal to that experienced by patients with 3-vessel coronary artery disease.[5]

Studies in recent years have shown that up to 30% to 50% of patients with CIU have autoantibodies to the α-chain of the high-affinity receptor for IgE (FcεRIα).[6] Therefore, a high proportion of CIU is now thought to be an intrinsic autoimmune condition. It is hypothesized that these IgG autoantibodies react specifically with the FcεRIα on dermal mast cells and basophils, evoking release of histamine and other mediators, which cause urticaria and angioedema, although conclusive proof of this mechanism in vivo has not yet been reported. Further evidence to support an autoimmune basis for urticaria in some patients is the close association with thyroid autoimmunity (TA).[7] Such patients have autoantibodies directed against thyroid proteins but may be euthyroid. However, there is conflicting evidence that treating the underlying thyroid dysfunction alters the course of the accompanying urticaria.[8,9]

The severity and clinical pattern of CIU can vary considerably from patient to patient, resulting in treatment regimens that need to be individualized. Antihistamines are the cornerstone of the therapeutic approach. Although short tapering courses of oral corticosteroids may be reasonable in emergency situations, long-term corticosteroid therapy can have serious associated adverse effects and is recommended only

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when absolutely necessary.[10] Alternative immunomodulatory options include but are not limited to cyclosporine, mycophenolate, intravenous gamma globulin, and plasmapheresis.[11–13] This retrospective analysis sought to collect and summarize the baseline demographic, laboratory, and clinical characteristics in a large cohort of patients with CIU and to review the various medication groups used to treat the study population. A particular interest of the study was to evaluate the relationship of CIU to functional autoantibodies against the FcεRIα and the association with TA.

METHODS

Study Design

Patients who met the diagnostic criteria for CIU and who were evaluated between April 1, 2006, and March 31, 2008, at the Division of Allergy and Inflammation, Beth Israel Deaconess Medical Center, Harvard Medical School, were included in the study, and the clinical records were extensively evaluated retrospectively.

Patient Selection

Individuals were included in this study if they had CIU, ie, episodes of hives (characteristic wheal and flare of <24–48 hours' duration), occurring at least 3 times a week for at least 6 weeks without an identifiable exogenous cause. Other forms of CU, such as physical, drug-induced, cholinergic, and acute urticaria, were excluded. Systemic disease and dermatologic disease that could have interfered with evaluation of the symptoms (such as erythema multiforme, bullous pemphigoid, dermatitis herpetiformis, mastocytosis/urticaria pigmentosa, pruritic urticarial papules, and plaques of pregnancy) were also criteria for exclusion. Patients with a possible infectious cause of their urticaria (such as *Helicobacter pylori*, hepatitis B and C, Epstein-Barr virus, and herpes) were also excluded. Patients with documented vasculitis on skin biopsy specimens were excluded, but some patients with features of vasculitis but not meeting the full pathologic criteria for vasculitis were included (n = 4). A detailed review of the clinical records of more than 500 patients seen for urticaria was performed, resulting in the selection of 236 study participants based on the inclusion criteria. The study protocol had the full approval of the institutional review board of Beth Israel Deaconess Medical Center.

Methods

Clinical and laboratory data pertaining to baseline characteristics, treatment modalities used, and treatment responses were collected via medical record review, were entered into a database program (Microsoft Excel 2003; Microsoft Corp, Redmond, Washington), and were compiled for analysis. Collection of data from the clinical evaluation focused particular attention on the severity and distribution of body areas affected by CIU, along with associated conditions, such as angioedema and dermographism. Collection of data from the laboratory evaluation included a review of all tests performed as part of the urticaria workup. These tests generally included a complete blood cell count with a differential count, erythrocyte sedimentation rate, anti–thyroid peroxidase antibodies, antithyroglobulin antibodies, and thyrotropin, at a minimum. Results of the autologous serum skin test (ASST) and the basophil activation test (BAT-CD203) were also included in the analysis. For BAT-CD203, the samples from patients seen during this period were sent to the Clinical Reference Laboratories at National Jewish Medical and Research Center, Denver, Colorado, where measurement of donor basophil CD203 expression was used as a basophil activation marker, and more than 5% cell surface expression was reported as positive[14] (test name "anti-FcεR1 antibody"; test code IGERAB). Because of the retrospective nature of the study, certain laboratory tests were not available for all patients.

A detailed analysis of all the agents used for treatment was performed, which included determination of the various groups of the administered medications, the average number of medications from all the various groups used in the study cohort, and the maximum number of medications from various groups used simultaneously. Various correlations of the treatment patterns among subgroups of patients based on demographic distributions and duration of disease activity were also performed. Nonparametric comparisons of group means were made using the Mann-Whitney test. Proportions were compared using the χ^2 test. $P < .05$ was considered significant for all tests.

RESULTS

Baseline Characteristics

Of the 236 patients with CIU, 181 were females (77%) and 55 were males (23%) (Table 1). The mean patient age at the time of evaluation was 39 years (range, 16–87 years) for females and 43 years (range, 19–78 years) for males. The mean duration of symptoms before evaluation was 35.6 months (range, 0.25–552 months) in females and 30.8 months (range, 0.25–216 months) in males. Eighty-three of the 236 patients (35%) exhibited angioedema along with urticaria, which was less than expected.[1] Sixty-one females (73%) and 22 males (27%) had associated angioedema, which was proportional to the overall sex distribution. Associated dermographism was present in 58 patients (25%), of which 41 were females (71%) and 17 were males (29%), also in correlation with the overall sex distribution. Thirty-seven of 211 patients (18%) who were tested for erythrocyte sedimentation rate had a raised

Table 1. Baseline Characteristics of the Study Population

Characteristic	Females	Males	Total
Patients, No (%)	181 (77)	55 (23)	**236**
Age, mean, y	39	43	40
Duration of urticaria before diagnosis, mean, mo	35.6	30.8	34.5
Associated angioedema, %	34	40	35
Associated dermographism, %	23	31	25

value at the time of diagnosis (defined as >20 mm/h). Patients with a raised erythrocyte sedimentation rate showed a similar distribution in the group with only urticaria (18%) and in the group with urticaria along with associated angioedema (16%).

Frequency of Autoantibodies

The gold standard for detecting autoantibodies to the FcεRIα in CIU is the functional in vitro donor basophil histamine-releasing activity (HRA) assay.[15,16] BAT-CD203 (measuring CD203 expression) was used as a marker to identify autoantibodies to the FcεRIα considering the reasonable correlation of BAT-CD203 with HRA cited in the literature ($r = 0.6$; $P = .001$; sensitivity = 77%; specificity = 82%; positive predictive value = 83%; and negative predictive value = 75%).[14] BAT-CD203 was measured in 58 of the 236 patients using an assay offered by a commercial laboratory (see the "Methods" section), and the results were found to be positive in 20 patients (34%) (Table 2). Of the 50 female and 8 male patients tested for BAT-CD203, a larger proportion of females demonstrated evidence of autoimmunity, with 38% of females (n = 19) and 13% of males (n = 1) showing a positive result. TA was tested in 146 females and 42 males and was defined by the presence of elevated levels of either or both anti–thyroid peroxidase antibodies (>35 IU/mL) and antithyroglobulin antibodies (>40 IU/mL). TA was found to be present in 34% of females (n = 50) and in 17% of males (n = 7). Because the number expected by chance alone was 11, given that less than 6% of healthy individuals have TA, the association proves significant for males and females ($P < .01$). Evidence of TA was present in 47% of BAT-CD203–positive females (n = 9), and there was no evidence of TA in the 1 BAT-CD203–positive male tested. Conversely, 37% of BAT-CD203–negative females (n = 11) and 14% of BAT-CD203–negative males (n = 1) had TA. There was no statistically significant correlation between the presence of TA and evidence of basophil activation in patients tested for TA and BAT-CD203.

Owing to the availability of in vitro assays in the past 2 years, ASST was less frequently performed than it was previously, particularly owing to the technical challenges of performing skin testing in patients with CU, including the confounding nature of concomitant dermographism and the need to stop antihistamine treatment to obtain reliable skin test results. Therefore, only 8 patients, 7 females and 1 male, underwent ASST. Four of the 7 females had positive test results (57%), whereas the only male patient who underwent ASST showed a negative result. Correlations among ASST, BAT-CD203, and TA results are given in Table 3. The small number of patients who underwent ASST renders the results insufficient to draw any meaningful conclusions.

Serum IgE level was measured in 105 of the 236 patients and was found to be elevated (≥200 kU/L) in 25 (24%). Four of 10 patients (40%) with an elevated IgE level showed a positive BAT-CD203 result, whereas 13 of 34 patients (38%) with a normal IgE level showed a positive BAT-CD203 finding (Table 4). The results, therefore, seem to show no correlation between BAT-CD203 results and IgE level. Antinuclear antibodies (ANAs) were tested in 69 patients (57 females and 12 males). A positive result was found in 22 patients (32% of females and 33% of males). A detailed description of all the ANA-positive patients according to the titer measurement and the presence of basophil activation or TA is given in Table 5. No correlations were found between ANA and BAT-CD203 or between ANA and TA (Table 5).

Treatment Analysis

The wide range of disease severity in this patient population resulted in a variety of treatment regimens. However, antihistamines remained the mainstay of treatment, with the addition of prednisone and other agents when a more aggressive approach was required to control the symptoms (Table 6). H_1 antagonist monotherapy was used and continued in 83 of 225 patients (37%). Second-generation H_1 antagonists, which are long acting and minimally sedating, were generally used as first-line agents, with the first-generation H_1 antagonists added only if the disease was not controlled with use of the second-generation H_1 antagonists or H_2 antagonists. Combined H_1 and H_2 antagonists were administered to 80 of 225 patients (36%).

Patients with CIU who had not responded to H_1 antagonists (even in high doses), either alone or combined with H_2 antagonists, used corticosteroids or cyclosporine. Prednisone/cyclosporine was used in addition to H_1 antagonists in 23 of 225 patients (10%) and in addition to $H_1 + H_2$ antagonists in

Table 2. Laboratory Test Results in the Study Population

Characteristic	Patients, No./total No. (%)		
	Females	Males	Total
BAT-CD203+	19/50 (38)	1/8 (13)	**20/58** (34)
TA+	50/146 (34)	7/42 (17)	**57/188** (30)
ANA+	18/57 (32)	4/12 (33)	**22/69** (32)
ASST+	4/7 (57)	0/1	**4/8** (50)
Serum IgE ≥200 kU/L	17/82 (21)	8/23 (35)	**25/105** (24)

Abbreviations: ANA, antinuclear antibody; ASST, autologous serum skin test; BAT-CD203, basophil activation test; TA, thyroid autoimmunity; +, positive.

Table 3. Results of Autoimmunity Studies[a]

	BAT-CD203+ (n = 20)	BAT-CD203− (n = 38)[b]	ASST+ (n = 4)	ASST− (n = 4)[c]
TA+	9 (45)	12 (32)	0	0
TA−	11 (55)	25 (68)	4	3

Abbreviations: ASST, autologous serum skin test; BAT-CD203, basophil activation test; TA, thyroid autoimmunity; +, positive; −, negative.

[a] Data are given as number (percentage) of patients.

[b] One female had a negative BAT-CD203 result but no thyroid antibody value.

[c] Thyroid autoantibodies were not tested for in 1 ASST− patient (female).

Table 4. Correlations Among BAT-CD203, ASST, and Serum IgE[a]

	ASST+ (n = 3)[b]	ASST− (n = 1)[b]	Serum IgE ≥200 kU/L (n = 10)	Serum IgE <200 kU/L (n = 34)
BAT-CD203+	1	0	4 (40)	13 (38)
BAT-CD203−	2	1	6 (60)	21 (62)

Abbreviations: ASST, autologous serum skin test; BAT-CD203, basophil activation test; +, positive; −, negative.

[a] Data are given as number (percentage) of patients.

[b] Only 1 ASST− and 3 ASST+ patients were tested for BAT-CD203 (all were females).

39 of 225 patients (17%). Prednisone or cyclosporine was used in 28% of patients. Additional third-line agents were administered in patients with severe CIU who were nonresponsive to the previously mentioned medications. Such third-line pharmacotherapy options were used with or without prednisone/cyclosporine in 37 of 225 patients (16%). These agents mainly included thyroxine and leukotriene receptor antagonists, with rare use of agents such as intravenous gamma globulin, mycophenolate, colchicine, and hydroxychloroquine.

Additional pharmacotherapy agents tended to be added in a step-up manner as needed to control the disease. Thus, the treatment regimens ranged from H_1 antagonist monotherapy to therapy with multiple agents, including prednisone, cyclosporine, and other third-line agents. The maximum number of agents administered to a patient to control disease symptoms at any time during treatment was recorded. The control of disease symptoms was determined clinically and resulted in stepping up (increasing doses to published maximums or adding another agent) or stepping down (decreasing doses or discontinuing use of an agent) medical therapy. The maximum number of agents used ranged from 1 to 7, with a mean of 2.6 for 225 patients. Patients with urticaria alone required an average of 2.4 agents, whereas patients with associated angioedema required 2.9 agents ($P < .01$).

Analysis was also performed for the number of agents used in subgroups of patients based on the duration of symptoms (Table 7). There seemed to be no correlation between duration of symptoms and the maximum number of medications used or between duration of symptoms and use of prednisone/cyclosporine.

The maximum number of medications used and the use of prednisone/cyclosporine were also studied in subgroups based on the presence or absence of basophil activation and TA. The results showed a trend toward more medications used in the BAT-CD203– and TA-positive subgroups (BAT-CD203 positive = 3.7, BAT-CD203 negative = 3.2; TA positive = 2.8, and TA negative = 2.6) and a similar greater use of prednisone/cyclosporine (BAT-CD203 positive = 60% of patients, BAT-CD203 negative = 58%; TA positive = 40%, and TA negative = 28%); however, the differences were not statistically significant. Use of multiple agents in subgroups based on patient age was also studied (Table 8). The data suggest that more agents were used to control CIU in patients older than 55 years compared with the other age groups ($P < .01$).

DISCUSSION

This study shows a 30% frequency of TA in patients with CIU, which is higher than that previously reported. In early studies,[9] the frequency of TA in patients with CIU is 12% to 20%, but some recent studies[17,18] showed a frequency as high as 20% to 30%. The frequency of TA was seen to be higher in females (34% in females compared with 17% in males). This is in accord with findings of a higher prevalence of TA in women in cross-sectional studies.[19] Other investigators[20] have also shown that the association of CIU with TA is higher in females. The mechanism whereby TA is associated with CIU is poorly understood. The presence of elevated antithyroid antibody levels may not be directly involved in the mast cell degranulation and pathogenesis of CIU but may serve only as a marker of autoimmunity.

The present study shows that approximately 34% of patients with CIU and available results exhibit autoantibodies to the FcεRIα (as identified using BAT-CD203), and the frequency was found to be higher in females. This finding corresponds to the considerable evidence that up to 30% to 50% of patients with CIU have autoantibodies to the FcεRIα.[6] In approximately 5% of patients with CIU demonstrating autoimmunity by means of ASST, there is no evidence of autoantibody to the FcεRIα, and in these cases, it is thought that the serum may contain autoantibodies to the IgE molecule itself.[6] However, there is currently no commercially available assay for these anti–IgE antibodies.

Results of previous studies[21] have suggested that there is a close association between TA (or abnormal thyroid function) and HRA. We used donor basophil CD203 expression as a marker to identify autoantibodies to the FcεRIα considering its reasonable correlation with HRA ($r = 0.6$; $P = .001$; sensitivity = 77%; specificity = 82%; positive predictive value = 83%; and negative predictive value = 75%)[14]; however, we found no significant correlation between CD203 upregulation and TA in patients tested for both. No previous data are available for the correlation between CD203 upregulation and TA in patients with CIU. However, some other recent studies[22] have also failed to show a strong relationship between HRA and TA. We also found no relationship between ANAs and BAT-CD203.

The associations of angioedema and dermographism with CIU have been documented to be 50% for each condition.[1,23] The present study showed a lower rate of association, with angioedema being present in 35% of the study population (n = 83) and dermographism in approximately 25% (n = 58).

Cyclosporine or corticosteroids were used in 28% of the study population, with another 16% requiring a trial of additional agents (such as thyroxine, intravenous gamma globulin, colchicine, antileukotrienes, hydroxychloroquine, and mycophenolate) used with or without prednisone/cyclosporine. This shows that in more than a quarter of the patients

Table 5. Correlations Among ANA, BAT-CD203, and TA[a]

ANA titer	Patients, total (F/M), No.	BAT-CD203+	BAT-CD203−	TA+	TA−
Negative	47 (39/8)	7/19 (37)	12/19 (63)	16/47 (34)	31/47 (66)
Positive	22 (18/4)	4/11 (36)	7/11 (64)	7/21 (33)	14/21 (67)
1:40	11 (10/1)	1/6[b]	5/6	4/10	6/10
1:80	5 (4/1)	2/3	1/3	1/5	4/5
1:160	3 (2/1)	1/2	1/2	1/3	2/3
1:320	2 (2/0)	0	0	0/2	2/2
Unknown	1 (0/1)	0	0	1/1	0/1

Abbreviations: ANA, antinuclear antibody; BAT-CD203, basophil activation test; TA, thyroid autoimmunity; +, positive; −, negative.
[a] Data are given as number (percentage) of patients.
[b] 1/6 means 1 of 6 patients with 1:40 ANA titer who were tested for BAT-CD203.

Table 6. Pattern of Medication Use

Medications	Study population, No. (%)
H_1 antagonists (as sole agents)	83 (37)
H_1 + H_2 antagonists (combined)	80 (36)
H_1 antagonists + prednisone/cyclosporine	23 (10)
H_1 + H_2 antagonists + prednisone/ cyclosporine	39 (17)
Patients receiving prednisone/cyclosporine, total	63 (28)
Other agents (used with or without prednisone/cyclosporine)	37 (16)
Maximum No. of agents used in the study population (n = 225), mean (range)	2.6 (1–7)

Table 7. Pattern of Medications Used Based on the Duration of Urticaria Symptoms

Duration of symptoms, mo	Patients, No.	Maximum No. of agents used	Use of prednisone/ cyclosporine, %
0–6	110	2.5	29
>6–12	34	2.7	21
>12–60	40	2.4	14
>60	36	2.8	30

Table 8. Number of Medications Used Based on Patient Age

Patient age, y	Patients, No.	Maximum No. of agents used
15–34	98	2.4
35–54	92	2.4
≥55	35	3.4[a]

[a] Statistically significant at $P < .01$.

with CIU, adequate control of disease symptoms is not achieved with antihistamine therapy alone and that additional pharmacotherapy options need to be used. We did not have sufficient data available to evaluate the efficacy of each particular agent.

The present data demonstrate that prednisone/cyclosporine was more likely to be used in the first 6 months or after 5 years of disease duration (approximately 29%–30% of patients each). The present study also reveals that significantly more therapeutic agents were used in older patients (≥55 years) compared with younger age groups. However, the retrospective nature of this analysis makes it difficult to draw meaningful conclusions.

TA or the presence of autoantibodies to the FcεRIα (as measured using a reasonably representative assay) is often considered to be evidence of an autoimmune cause of CIU, and these cases are often considered to be more difficult to control.[24,25] However, the present study found that patients with TA or CD203 upregulation did not require significantly more agents to control their symptoms than did patients without TA or CD203 upregulation. The exact role of autoantibodies to the FcεRIα or IgE in the pathogenesis of CIU has not yet been fully elucidated. It is still possible that TA and HRA are epiphenomena associated with CIU but that they are not directly involved in the pathogenesis of the disease.

Although the present study has limitations owing to its retrospective design (with missing data points for some patients) and its potential for selection bias in what tests were performed in which patients (because there were no prospective protocols for the use of diagnostic tests such as BAT-CD203, anti–thyroid peroxidase/antithyroglobulin antibodies, and ASST), it provides insight into the demographic distribution, clinical presentation, pertinent laboratory findings, and pattern of treatment options used to control CIU. Furthermore, this study highlights the need for a large-scale, prospective study of patients with CU to fully evaluate the correlations between positive test values and responders to individual therapies, which may help develop detailed treatment algorithms for this disorder.

REFERENCES

1. Champion RH, Roberts SOB, Carpenter RG, et al. Urticaria and angioedema: a review of 554 patients. *Br J Dermatol*. 1969;81:588–597.
2. Gaig P, Olona M, Munoz Lejarazu D, et al. Epidemiology of urticaria in Spain. *J Investig Allergol Clin Immunol*. 2004;14:214–220.
3. Jiamton S, Swad-Ampiraks P, Kulthanan K, et al. Urticaria and angioedema in Siriraj medical students. *J Med Assoc Thai*. 2003;86:74–81.
4. Vazquez Nava F, Almeida Arvizu VM, Sanchez Nuncio HR, et al. Prevalence and potential triggering factors of chronic urticaria and angioedema in an urban area of northeastern Mexico. *Rev Alerg Mex*.

2004;51:181–188.
5. O'Donnell BF, Lawlor F, Simpson J. The impact of chronic urticaria on the quality of life. *Br J Dermatol.* 1997;136:197–201.
6. Kaplan AP. Chronic urticaria: pathogenesis and treatment. *J Allergy Clin Immunol.* 2004;114:465–474.
7. Leznoff A, Josse RG, Denburg J. Association of chronic urticaria and angioedema with thyroid autoimmunity. *Arch Dermatol.* 1983;119: 636–640.
8. Rumbyrt JS, Katz JL, Schocket AL. Resolution of chronic urticaria in patients with thyroid autoimmunity. *J Allergy Clin Immunol.* 1995;96: 901–905.
9. Leznoff A, Sussman GL. Syndrome of idiopathic chronic urticaria and angioedema with thyroid autoimmunity: a study of 90 patients. *J Allergy Clin Immunol.* 1989;84:66–71.
10. Kaplan AP. Chronic urticaria and angioedema. *N Engl J Med*. 2002; 346:175–179.
11. Toubi E, Blant A, Kessel A, et al. Low-dose cyclosporine in the treatment of severe chronic idiopathic urticaria. *Allergy*. 1997;52: 312–316.
12. O'Donnell BF, Barr RM, Black AK, et al. Intravenous immunoglobulin in autoimmune chronic urticaria. *Br J Dermatol*. 1998;138:101–106.
13. Grattan CE, Francis DM, Slater NG, et al. Plasmapheresis for severe unremitting chronic urticaria. *Lancet*. 1992;339:1078–1080.
14. Yasnowsky KM, Dreskin SC, Efaw B, et al. Chronic urticaria sera increase basophil CD203c expression. *J Allergy Clin Immunol*. 2006; 117:1430–1434.
15. Soundararajan S, Kikuchi Y, Joseph K, et al. Functional assessment of pathogenic IgG subclasses in chronic autoimmune urticaria. *J Allergy Clin Immunol*. 2005;115:815–821.
16. Kikuchi Y, Kaplan AP. Mechanisms of autoimmune activation of basophils in chronic urticaria. *J Allergy Clin Immunol*. 2001;107: 1056–1062.
17. Verneuil L, Leconte C, Ballet JJ, et al. Association between chronic urticaria and thyroid autoimmunity: a prospective study involving 99 patients. *Dermatology*. 2004;208:98–103.
18. Palma-Carlos AG, Palma-Carlos ML. Chronic urticaria and thyroid auto-immunity. *Eur Ann Allergy Clin Immunol*. 2005;37:143–146.
19. Saravanan P, Dayan CM. Thyroid autoantibodies. *Endocrinol Metab Clin North Am*. 2001;30:315–337.
20. Gaig P, Garcia-Ortega P, Enrique E, et al. Successful treatment of chronic idiopathic urticaria associated with thyroid autoimmunity. *J Invest Allergol Clin Immunol*. 2000;10:342–345.
21. Kikuchi Y, Fann T, Kaplan AP. Antithyroid antibodies in chronic urticaria and angioedema. *J Allergy Clin Immunol.* 2003;112:218.
22. Altrich M, Halsey J, Altman L. Comparison of the in vivo autologous skin test with the in vitro diagnostic tests for diagnosis of chronic autoimmune urticaria. *Allergy Asthma Proc*. 2008;29:5.
23. Najib U, Sheikh J. An update on acute and chronic urticaria for the primary care provider. *Postgrad Med*. 2009;121:141–151.
24. Caproni M, Volpi W, Giomi B, et al. Chronic idiopathic and chronic autoimmune urticaria: clinical and immunopathological features of 68 subjects. *Acta Derm Venereol*. 2004;84:288–290.
25. Sabroe RA, Greaves MW. Chronic idiopathic urticaria with functional autoantibodies: 12 years on. *Br J Dermatol*. 2006;154:813–819.

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