

Association of Chronic Urticaria with Rheumatic Diseases and Thyroid Autoimmunity

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Abstract

Autoimmunity plays a major role in the pathogenesis of chronic urticaria (CU). CU has been reported to be associated with autoimmune thyroiditis and several rheumatic diseases in the related literature. This study aims to determine the clinical and laboratory features of CU in Taiwan, and to detect the association of CU with rheumatic diseases and thyroid autoimmunity. We reviewed the medical records of 106 patients who were diagnosed with CU at Changhua Christian Hospital during the period of September 2008 - August 2009. The female-to-male ratio was 2.1 : 1. The mean age at diagnosis was 36.5 years. Concomitant angioedema, dermographism and pressure-induced hive occurred in 23.1%, 26.7% and 68.1% of patients, respectively. Antithyroid antibodies (antithyroglobulin and/or antimicrosomal antibodies) presented in 20.6% of patients. Antinuclear antibodies (ANA), anti-SSA and anti-SSB antibodies presented in 10.4%, 7.2% and 1.4% of patients, respectively. Elevated erythrocyte sediment rate (ESR) was measured in 18.5% of patients. Twenty-eight patients (26.4%) had rheumatic diseases and/or thyroid autoimmunity. Of 16 patients with rheumatic diseases, Sjogren's syndrome and rheumatoid arthritis accounted for the majority. Patients with rheumatic diseases had higher prevalence of arthralgia ($p < 0.005$), ESR elevation ($p < 0.05$) and ANA positivity ($p < 0.005$) than patients without rheumatic diseases. A subgroup of CU has associations with rheumatic diseases and thyroid autoimmunity. Screen tests for autoimmune diseases in CU patients are recommended. (J Intern Med Taiwan 2010; 21: 277-284)

Key Words : Chronic urticaria; Rheumatic disease; Thyroid autoimmunity; Antinuclear antibodies

Introduction

Urticaria is a common disease that affects 15-25% of the population at some time in their lives¹. Chronic urticaria (CU) is defined as when wheals continuously or intermittently present for at least 6 weeks. The troublesome itching and skin lesions usually impair quality of life. The etiologies

of CU are heterogeneous. Less than 5% of CU cases are caused by allergy, especially sensitivities to food additives and drugs taken daily. Up to 90% of CU cases have no external cause related to their condition, are classified as idiopathic². The association of CU with *Helicobacter pylori* infection is controversial. Some reports^{3,4} suggest that CU as

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a consequence of *Helicobacter pylori* infection, but others⁵⁻⁷ deny this hypothesis. Recent studies have shown that approximately 30-50% of these chronic idiopathic urticaria patients have evidences of autoimmunity, so-called autoimmune urticaria⁸. In this subgroup of CU, patients have either serum IgG autoantibody direct to the α subunit of IgE receptor or functional anti-IgE autoantibody, which stimulate histamine release of mast cell and basophil^{9,10}.

The early studies indicated the association of chronic urticaria with thyroid autoimmunity, provide an indirect evidence of autoimmune origin in CU^{11,12}. In addition to thyroid autoimmunity, systemic lupus erythematosus (SLE), juvenile rheumatoid arthritis, insulin-dependent diabetes mellitus and celiac disease have been reported in association with CU¹³. To date, the prevalence of rheumatic diseases and thyroid autoimmunity in CU patients in Taiwan is still unknown. The aim of our study is to evaluate the association of CU with rheumatic diseases and thyroid autoimmunity.

Patients and methods

Patients

We analyzed the medical records of 106 patients who were diagnosed with CU in the rheumatology section of Changhua Christian Hospital from September 2008 - August 2009. For all patients, the primary reason for seeking medical care was for urticaria. All patients had continuous urticaria activity for at least 6 weeks when they first time visited our outpatient department. Those with physical urticaria were excluded from this study. The clinical and serological characteristics of each patient were obtained at the first visit.

Every patient was examined for the symptoms and signs of rheumatic diseases. A patient would be diagnosed with a definite rheumatic disease if he or she fully matched the diagnostic criteria of that disease; for example, 1997 revised American College of Rheumatology (ACR) classification

criteria for SLE¹⁴, 1987 ACR criteria for RA¹⁵, 2002 European criteria for Sjogren's syndrome (SS)¹⁶, 1984 modified New York criteria for ankylosing spondylitis (AS)¹⁷, 1992 Yamaguchi's criteria for adult-onset Still's disease (AOSD)¹⁸, 1980 ACR criteria for progressive systemic sclerosis (PSS)¹⁹, and 1990 International Study Group criteria for Behcet's disease²⁰. The definition of fever was eardrum temperature above 37.5°C while wheals appeared. The definition of arthralgia was defined as pain over either small joints or large joints of four limbs while wheals appeared. Dermographism was defined as immediate linear erythematous wheal after stroking the skin of forearm observed by physician. Pressure-induced hives were defined as the appearance of wheals over pressure bearing areas observed by physician. Angioedema was defined as swelling of deeper skin layers and mucosal tissue, and often involved the face, eyelids, lips, tongue or distal extremities. The information of angioedema was obtained by history or by physician's observation.

Laboratory tests

Antinuclear antibodies (ANA) in sera were screened against Hep-2 cells by indirect immunofluorescence (IIF) assay (DiaSorin, Stillwater, MN, USA). The presence of ANA was defined as titers $\geq 1 : 160$. Anti-SSA and anti-SSB antibodies were detected using the multiplexed immunoassay (AtheNA Multi-Lyte ANA-II Plus Test System, Zeus Scientific, USA) with manufacturer's instruction. The cut-off value for both anti-SSA and anti-SSB antibodies was 100 AU/mL. Patients with low titer ANA ($\leq 1 : 80$) but presence of anti-SSA and/or anti-SSB antibodies were considered to be ANA-positive. Antithyroglobulin antibodies (ATA) were detected using particle agglutination assay (FTI-SERODIA-ATG, Fujirebio Taiwan). The presence of ATA was defined as titers $\geq 1 : 400$. Antimicrosomal antibodies (AMiA) were detected using the enzyme-linked immunosorbent assay

(Abbott AxSYM system, Abbott Diagnostics, USA). The cut-off value for AMiA was 12 IU/mL. The diagnosis of thyroid autoimmunity was based on the presence of either ATA, AMiA, or both. Erythrocyte sedimentation rate (ESR) was measured using the modified Westergren system (Greiner Bio-One GmbH, Austria). The normal upper limit of ESR was 20 mm/hour. For elder patients, the normal upper limit of ESR should be corrected by age according to the formula: age (years) divided by 2 for men; age plus 10 then divided by 2 for women²¹.

Statistical analysis

All statistic analyses were computed using SPSS version 10.0 (SPSS Inc., USA). Quantitative variables are expressed as means \pm standard deviation, and were compared using ANOVA and Post HOC tests. Qualitative variables were compared using χ^2 test, with Fisher's exact test when appropriate. All statistical analyses were two-tailed and p values <0.05 were considered to be significant.

Results

Clinical and laboratory features

The clinical features of 106 patients with CU are summarized in table 1. Seventy-two (67.9%) patients were female. The female-to-male ratio was 2.1 to 1. The mean age at diagnosis was 36.5 ± 12.3 years (range 15-71 years). Only 4 patients had age above 60 years. The mean disease duration at diagnosis was 100.3 weeks (range 6-2085 weeks). Concomitant angioedema occurred in 24 of 104 (23.1%) patients. Dermographism was observed in 23 of 86 (26.7%) patients. Pressure-induced hives were observed in 47 of 69 (68.1%) patients. Three of 106 (2.8%) patients had associated fever, and 15 of 106 (14.2%) patients had associated arthralgia.

Table 2 summarizes the laboratory features in patients with chronic urticaria. ATA presented in 9 of 63 (14.3%) tested patients, and AMiA presented

Table 1. Clinical features in patients with chronic urticaria

	Total patients n=106
Sex (female/male ratio)	2.1
Age at diagnosis (year)(mean \pm SD)	36.5 ± 12.3
Disease duration at diagnosis (week) (mean \pm SD)	100.3 ± 237.5
Angioedema (n positive/n tested)(%)	24/104(23.1)
Dermographism (n positive/n tested)(%)	23/86(26.7)
Pressure-induced hive (n positive/n tested)(%)	47/69(68.1)
Fever (n positive/n tested)(%)	3/106(2.8)
Arthralgia (n positive/n tested)(%)	15/106(14.2)

SD: standard deviation.

Table 2. Laboratory features in patients with chronic urticaria

	Total patients n=106
ATA(n positive/n tested)(%)	9/63(14.3)
AMiA(n positive/n tested)(%)	7/63(11.1)
ANA(n positive/n tested)(%)	10/96(10.4)
Anti-SSA(n positive/n tested)(%)	5/69(7.2)
Anti-SSB(n positive/n tested)(%)	1/69(1.4)
ESR elevation(n positive/n tested)(%)	17/92(18.5)

1. Thirteen (20.6%) of 63 tested patients had positivity of either ATA, AMiA or both.

2. ATA: antithyroglobulin antibody, AMiA: antimicrosomal antibody, ANA: antinuclear antibody, ESR: erythrocyte sediment rate.

in 7 of 63 (11.1%) tested patients. All together, 20.6% of the tested patients had either ATA, AMiA or both. The positivity of ANA, anti-SSA and anti-SSB in our patients was 10.4%, 7.2% and 1.4% respectively. Elevated erythrocyte sediment rate (ESR) was measured in 18.5% of the patients.

Table 3 summarizes the case number of rheumatic diseases and thyroid autoimmunity in our patients. Sixteen patients (15.1%) had rheumatic diseases which included SS (n=5), RA (n=3), SLE (n=2), AS (n=2), PSS (n=1), palindromic rheumatism (n=1), Behcet's disease (n=1) and AOSD (n=1). Thirteen patients (12.3%) had thyroid autoimmunity, of them, one had concomitant SS. One patient had vitiligo (not listed in table 3). In summary, total 28 patients with rheumatic diseases

Table 3. Rheumatic diseases and thyroid autoimmunity in 106 patients with chronic urticaria

Disease	Number of patients
Rheumatic diseases	16
Sjogren's syndrome	5
Rheumatoid arthritis	3
Systemic lupus erythematosus	2
Ankylosing spondylitis	2
Progressive systemic sclerosis	1
Palindromic rheumatism	1
Behcet's disease	1
Adult-onset Still's disease	1
Thyroid autoimmunity	13

1. One patient had both Sjogren's syndrome and thyroid autoimmunity.

2. Twenty-eight patients with rheumatic diseases and/or thyroid autoimmunity accounted for 26.4% of whole chronic urticaria patients. Of these 28 patients, only 6 (21.4%) had known autoimmune disease before visiting our clinics due to urticaria problem.

and/or thyroid autoimmunity accounted for 26.4% of whole CU patients. Of these 28 patients, only 6 (21.4%) had known history of autoimmune disease before visiting our clinics due to urticaria problem.

Differences between the subgroups of CU patients

Our patients were divided into 3 subgroups: with rheumatic diseases (group A), with thyroid autoimmunity (group B), with neither rheumatic diseases nor thyroid autoimmunity (group C) (table 4). In comparison with group C, the patients in group A had higher prevalence of arthralgia (56.3% v.s 5.2%, $p < 0.005$), ESR elevation (43.8% v.s 15.9%, $p < 0.05$) and ANA positivity (66.7% v.s 0.0%, $p < 0.005$), while the patients in group B had lower prevalence of angioedema (0.0% v.s 28.0%, $p < 0.05$). The prevalence of fever in group A was higher than group C, but it was not statistically significant (12.5% v.s 1.3%, $p = 0.07$). In comparison with group B, the patients in group A had higher prevalence of arthralgia (56.3% v.s 7.7%, $p < 0.01$), ESR elevation (43.8% v.s 0.0%, $p < 0.01$) and ANA positivity (66.7% v.s 7.7%,

$p < 0.005$). There was no significant difference in sex, age, disease duration, dermographism and pressure-induced hive between any two of group A, B and C.

Discussion

This study presents the clinical and laboratory features of 106 patients with CU, and demonstrates the association of CU with rheumatic diseases and thyroid autoimmunity. CU is more common in the middle-aged women. The female predominance (female/male ratio of 2.1 : 1) in our patients was similar to that in the western countries^{11,22-24}. For the patients with autoimmunity evidenced by the presence of antithyroid antibodies or the positive histamine release test, the female/male ratio was more higher, ranged from 2.7 : 1 to 7 : 1^{11,12,22,23}. The mean age of our patients was 36.5 ± 12.3 years (range 15-71 years), which was comparable with previous reports^{22,25}. Only 4 (3.8%) patients were elderly and this may elucidate the rarity of CU in the elderly population. Angioedema is defined as nonpitting swelling of cutaneous and mucosal tissue and usually affects the deeper skin layer. Concomitant angioedema was not uncommon in our CU patients. In this study, dermographism was often observed in conjunction with CU. Pressure-induced hives were prevalent in CU patients.

Several studies have demonstrated the presence of autoantibodies in a subgroup of CU, named autoimmune urticaria. In 1983, Leznoff et al.¹¹ firstly observed an increased incidence (12.1%) of antithyroid antibodies in CU patients, compared with 3-6% in the general population. Since then the association of CU with autoimmune thyroiditis has been proposed by several studies^{12,22,24}. Kikuchi et al.²⁴ found antithyroid antibodies in 27.7% of histamine release-positive CU patients and 10.9% of histamine release-negative CU patients. Irinyi et al.²² found antithyroid antibodies in 11% of CU patients and in 23% of autoimmune urticaria

Table 4. Differences between the subgroups of chronic urticaria patients

	Group A (with RD) n=16	Group B (with TA) n=13	Group C (with neither RD nor TA) n=77	p value		
				A vs C	B vs C	A vs B
Sex (female/male ratio)	2.2	3.3	2.0	ns	ns	ns
Age at diagnosis (year)(mean \pm SD)	41.4 \pm 12.3	40.5 \pm 7.9	35.1 \pm 12.4	ns	ns	ns
Disease duration at diagnosis (week) (mean \pm SD)	115.4 \pm 205.6	122.4 \pm 230.1	102.6 \pm 257.3	ns	ns	ns
Angioedema (n positive/n tested)(%)	2/16(12.5)	0/13(0.0)	21/75(28.0)	ns	<0.05	ns
Dermographism (n positive/n tested)(%)	2/7(28.6)	4/11(36.4)	17/68(25.0)	ns	ns	ns
Pressure-induced hive (n positive/n tested) (%)	3/4(75.0)	8/10(80.0)	36/55(65.5)	ns	ns	ns
Fever (n positive/n tested)(%)	2/16(12.5)	0/13(0.0)	1/77(1.3)	ns	ns	ns
Arthralgia (n positive/n tested)(%)	9/16(56.3)	1/13(7.7)	4/77(5.2)	<0.005	ns	<0.01
ESR elevation (n positive/n tested)(%)	7/16(43.8)	0/13(0.0)	10/63(15.9)	<0.05	ns	<0.01
ANA (n positive/n tested)(%)	10/15(66.7)	1/13(7.7)	0/69(0.0)	<0.005	ns	<0.005

RD: rheumatic disease, TA: thyroid autoimmunity, ESR: erythrocyte sediment rate, ANA: antinuclear antibody, ns: no significance.

patients. Our study demonstrated a considerable prevalence (20.6%) of antithyroid antibodies in CU patients that linked CU and autoimmunity together. However, antithyroid antibodies (ATA, AMiA) themselves are not pathognomonic for CU. Some have speculated that antithyroid antibodies are merely markers of autoimmunity. Others have suggested that antithyroid antibodies cause inflammation in the thyroid, leading to a release of cytokines, which in turn decrease the threshold for mast cell degranulation².

Up to 30-50% of patients with CU have autoantibodies against the α chain of the high-affinity receptor for IgE (Fc ϵ RI) and 9% of patients with CU have functional anti-IgE antibodies²⁶. These pathogenic autoantibodies promote histamine release from mast cells and basophils. Further evidence has shown that classic complement activation in the presence of anti-Fc ϵ RI, with generation of C5a, augments histamine release from mast cells and basophils²⁷. The methods for detecting clinically relevant au-

toantibodies are autologous serum skin test and in vitro donor basophil histamine release assay²⁸. To date, this autoimmune-based pathogenesis may accounted for a half of CU patients, but the remainder still have an unknown mechanism for their urticaria.

The ANA positivity in our patients was 10.4%, which was slightly higher than 5% in normal individuals²⁹. The ANA positivity in CU has rarely been reported in English literature. Leznoff et al.¹² reported ANA positivity of 7.9% in CU patients with thyroid autoimmunity. The prevalence of anti-SSA and anti-SSB antibodies in our patients was 7.2% and 1.4%, respectively. The presence of ANA and anti-SSA/SSB antibodies implicates underlying rheumatic diseases, for example, SLE and SS. CU patients with rheumatic disease should be identified and treated with adequate disease-modifying antirheumatic drugs in addition to antihistamine.

Twenty-six percent of our patients had rheumatic diseases and/or thyroid autoimmunity, compared with 13-22% reported previously^{22,23}. Sabroe

et al.²³ reported that a history of autoimmune conditions was given significantly more often by patients with anti-Fc ϵ RI and/or anti-IgE autoantibodies than by those without autoantibodies. Autoimmune diseases reported by CU patients included autoimmune thyroiditis, vitiligo, rheumatoid arthritis, insulin-dependent diabetes mellitus and pernicious anemia^{22,23}. In our study, autoimmune thyroiditis (13/106), SS (5/106), RA (3/106), SLE (2/106) and AS (2/106) were most often associated with CU. Notably, most (78.6%) of our patients with systemic and/or thyroid autoimmunity did not have known history of autoimmune disease before visiting to our clinics due to urticaria problem. Thus the physicians should be alert to survey the possible autoimmunity in their CU patients. Complete history taking and physical examination for detecting autoimmune disease are important.

We investigated the clinical and laboratory characteristics of the subgroups of CU, and found that the patients with rheumatic diseases had significantly higher prevalence of arthralgia (56.3%), ESR elevation (43.8%) and ANA positivity (66.7%), compared with those without rheumatic diseases. On the other hand, the concomitant symptom of arthralgia and the laboratory findings of abnormal ESR and/or ANA in CU patients are clinical clues for associated rheumatic diseases, and indicate further rheumatologic evaluation.

This study has some limitations. First, patients who were referred to medical center more likely to have the severe form of CU, so our results may not demonstrate the real prevalence of rheumatic diseases and thyroid autoimmunity in general CU population. Second, the reason for the lower prevalence of concomitant angioedema in the subgroup of CU patients with thyroid autoimmunity was unclear, but may be the bias resulted from small case number. It needs large studies to determine the prevalence of concomitant angioedema in CU

patients with thyroid autoimmunity.

In conclusion, our study elucidates the clinical and laboratory features of CU, and the association of CU with rheumatic diseases and thyroid autoimmunity. Urticaria can precede, occur concomitantly with or appear after the diagnosis of autoimmune disease. We suggest performing complete history taking, physical examination and laboratory screen tests for autoimmune diseases in CU patients.

Conflict of interest

None.

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慢性蕁麻疹和風濕病及自體免疫 甲狀腺疾病之間的相關性

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摘 要

慢性蕁麻疹的致病機轉中，自體免疫扮有重要的角色。慢性蕁麻疹已被報告和自體免疫甲狀腺炎及數種風濕病有相關性。本研究的目的是在於了解台灣慢性蕁麻疹病人的臨床表徵和自體抗體，並探討慢性蕁麻疹和風濕病及自體免疫甲狀腺疾病之間的相關性。我們回顧2008年9月至2009年8月，於彰化基督教醫院過敏免疫風濕科診斷為慢性蕁麻疹，共106位病人。我們就臨床表徵、自體抗體和並存的自體免疫疾病予以分析。女性和男性的比例為2.1：1。平均診斷年齡為36.5歲。血管性水腫、皮膚劃紋症和壓力誘發之疹塊分別發生於23.1%、26.7%和68.1%的病人。20.6%的病人具有抗甲狀腺抗體（抗甲狀腺球蛋白抗體、抗微粒體抗體）。10.4%的病人具有抗核抗體，7.2%的病人具有SSA抗體，1.4%的病人具有SSB抗體。18.5%的病人其紅血球沉降速率升高。28位(26.4%)病人同時患有風濕病或自體免疫甲狀腺疾病二者之一。在16位合併風濕病的病人中，乾燥症和類風濕性關節炎共佔其中的一半。相較於沒有合併風濕病的病人，合併風濕病的病人其關節痛、高紅血球沉降速率和陽性抗核抗體的盛行率顯著較高（ p 值分別為 <0.005 、 <0.05 、 <0.005 ）。部分的慢性蕁麻疹和風濕病及自體免疫甲狀腺疾病有相關性。我們建議對慢性蕁麻疹病人進行自體免疫疾病的篩檢檢查。