MEDICUS

ISSN 1409-6366 UDC 61 Vol · 27 (1) · 2022

Original scientific paper

Profesional paper

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Case report

Medical Journal

MEDICUS

Original scientific paper

Profesional paper

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Case report

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ASST AND AUTOIMMUNITY IN PATIENTS WITH CHRONIC SPONTANEOUS URTICARIA

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Medicus 2022, Vol. 27 (1): 32-38

ABSTRACT

Objective: To invest possible association between HSU and: i) ASST ii) autoimmune diseases, iii) autoimmune serology, iv) atopy and dermographism.

Methods: This is a perspective study. Patients with CSU (chronic spontaneous urticaria) were studied. UAS7 was applied to all of them.ASST and the following blood analyses were performed: anti- TPO, anti-nuclear antibodies (ANA) and rheumatoid factor (RF).

Results: We analyzed 48 patients with CSU; most of them were women, angioedema was associated with CSU in more than half of the patients, ASST was positive in more than one third of the patients and almost the same number of patients had positive autoimmune status.Almost half of the patients had a personal history of atopy and presence of dermographism.

Conclusions: This study brings additional evidences of interest in patients with CSU as they could be associated to ASST and autoimmunity.

Keywords: Chronic spontaneous urticaria, ASST, autoimmunity

INTRODUCTION

Chronic spontaneous (idiopathic) urticaria (CSU), defined as the occurrence of wheals, angioedema, or both for more than 6 weeks, affects 1–2% of the population (1). Females are affected at least twice as often as males, and most patients are over 20 years of age (1). CSU represents an important burden that compromises patient's quality of life, interferes with routine daily activities (2).Several potential biomarkers for urticaria have been proposed, but only 5 of them have shown good clinical correlation: (3,4,5) Total serum IgE levels, C-reactive protein (CRP), Autologous serum skin test (ASST), Anti-thyroid peroxidase autoantibodies (IgG anti-TPO).Autoimmunity(ie, autoimmune mechanisms of skin mast cell activation) is held to be a frequent underlying cause of CSU(6).CSU is associated with autoimmunity in 30–45% of the cases, sharing some immunological mechanisms with other autoimmune diseases, and is associated with autoimmune thyroid disease (ATD) in about 4.3% –57.4% patients (9). It is determined that patients with CSU have higher levels of anti-thyroid peroxidase (anti-TPO) antibodies, antinuclear antibodies (ANA), antithyroglobulin (i.e., antimicrosomal) antibodies, rheumatoid factor, anti-transglutaminase IgA antibodies, and anti-parietal cell antibodies with anti-dsDNA, and anti-cardiolipin antibodies trending toward significance (7).Autoimmune chronic spontaneous urticaria (CSU) is due to mast cell (MC)-activating autoantibodies, which are screened for by the autologous serum skin test (ASST) and basophil tests (BTs).(8). The above-mentioned factors, alone or combined are often used to classify patients as autoimmune and non- autoimmune CSU.

MATERIALS AND METHODS

This prospective study was conducted from January 2021- November 2021 in the department of Dermatology in City General Hospital "8mi Septemvri", Skopje, North Macedonia. The study and the data collection were conducted with the approval of the institutional and ethical committee. Informed consent was obtained from all patients.

Patient selection and clinical data collection

Forty-eight adults and adolescents, 15-70 years of age, with a diagnosis of CSU, confirmed by a dermatologist according to the international Guideline 2013 (10), were included.

Inclusion criteria: Patients with active CSU.

Exclusion criteria: Patients with pure chronic inducible urticaria or bradykinin-mediated angioedema.

Also the medical history, including history of personal or familial atopy (asthma, atopic dermatitis and allergic rhinitis) and autoimmune diseases, as well as previous and current treatments for CSU were recorded.

The Weekly Urticaria Activity Score (UAS7) was used to assess disease activity (10). Patients were asked to record their symptoms for seven consecutive days prior to day of inclusion. Patients were classified as follows: severe CSU (UAS7 = 28-42), moderate CSU (UAS7 = 16-27), mild CSU (UAS7 = 7-15), well-controlled CSU (UAS7 = 1-6) and itch- and wheals- free (UAS7 = 0) (11).

Disease duration was defined as the time from the first onset of symptoms to day of inclusion. Recurring episodes of CSU, defined as recurrence of symptoms after at least 6 months of spontaneous remission, were also recorded.

For ASST and blood analyses, patients were considered as untreated, if they had stopped H1-antihistamines for at least 48 hours(12), anti-leukotrienes and H2-antihistamines for at least 7 days, and corticosteroids or cyclosporine

Autoimmunity

Autoimmunity was defined in the case of a personal history of autoimmune disease or in the presence of at least one type of autoimmune antibodies (AAbs) (included anti- TPO, anti-nuclear antibodies (ANA) and rheumatoid factor (RF)).

No autoimmunity was defined as the absence of autoimmune disease and AAbs.

Autologous skin serum test

ASST was performed on 48 untreated patients by the intradermal injection of 50 µL of the patient's own serum into the volar part of the forearm (12).

Positive control: Prick tests with histamine

Negative control:Intradermal injection of normal saline solution.

Positive test: appearanceof a red wheal with a diameter of 1.5 mm or greater than the wheal produced by the injection of normal saline solution within 20 minutes.

Patients were classified as having a positive or a negative ASST.

Biological tests

Blood analyses include the following autoimmune antibodies (AAbs): Anti-TPO, ANAand RF

Autoimmune Titers were considered positive if: Anti-TPO > 60 (0-60) U/ml, ANA > 1:160, and RF >15.9 (0-15.9)

Statistical analyses

Data for categorical variables are expressed as frequencies followed by the number of patients positive for this parameter in brackets over number of patients studied, and for continuous variables as mean ± standard deviation (SD) with minimum and maximum values in brackets.

RESULTS

Clinical data: This study included 48 patients with CSU, 34 of them were women (70,8%), and 14 of them were men (29.2%) (table 1,figure1), mean age in this study was 45.1 years (table 1) and mean duration of CSU in studied patients was 7.5 years (table 1).

Associations with angioedema: In this study angioedema was associated with wheals in 31 patients (64,5%) (table 1, figure 2).

Disease activity: Concerning disease activity based on UAS7 21/48patients (43.7%) had severe disease, 7/48patients (14.5 %) had moderate disease, 15/48 patients (31.2 %) had mild disease, 2/48 patients (4.1%) had well-controlled disease and 3/48 patients (6.5%) were itch-and wheals-free. (table 3, figure 3).

Associations with ASST: ASST was performed on 48 patients and 20of them (41.6%) were positive, and in 28 (58.4%) it was negative. (table 1,figure 4)

Associations with autoimmune disease: Considering the autoimmune status 17/48 patients (35,4%) had clinical history and/or serological markers of autoimmunity, and were considered as having a positive autoimmune status. (table 1, figure 5)

Personal history of autoimmune diseases was present in 13/48 patients (27%), familial history of autoimmune disease was found in 9/48 (18,7%) of cases(table 1, figure 6). In patients with personal history of autoimmune diseases Thyroiditis was found in 9/13 (69,2%), and Vitiligo was found in 4/13 (30,8 %)of the cases. (table 1, figure 7)

Associations withautoimmune serology: Considering autoimmune serology, anti-TPO was present in 10/48 (20,8 %) (table 2 , figure 8), ANA was present in 5/48 (10,4 %)(table 2, figure 9) and RF was present in 2/48 (4.1 %) (table 2, figure 10).

Associations withatopy and dermographism: Almost half of the patients 27/48 (56,3 %)had a personal history of atopy and 14/48 (29,1%) of the patients had familial history of atopy (based on anamnesis) (table1, figure 11).Presence of dermographism was confirmed in25/48 (52%) of the patients. (table 1, figure 12).

Tables

	N studied	Numbers (%) or mean ± SD (min-max)
Sex (female)	48	34 (70,8%)
Mean age (years)	48	41,5 years (15-68 years)
Disease duration	48	7,5 years (2 months-180 months)
Angioedema	48	31 (64,5%)
Symptomatic dermographism	48	25 (52%)
Personal history of atopy	48	27 (56,3%)
Familial history of atopy	48	14 (29,1%)
Personal history of concomitant autoimmune disease	48	13 (27%)
Thyroiditis	13	9 (69,2%)
Vitiligo	13	9 (30,8%)
Familial history of autoimmune disease	48	9 (18.7%)
Positivity of ASST	48	20 (41,6%)

Table 1: Clinical data of the cohort of patients with CSU.

	N studied	Numbers (%)	Reference value
Positivity of AAbs			
Anti-TPO	48	10 (20.8 %)	> 34 U/ml
ANA	48	5 (10,4 %)	> 1:160
Rheumatoid factor	48	2 (4,1 %)	RF > 1:40

Table 2:Titers for AAbswere considered positive if anti-TPO > 34 U/ml, ANA > 1:160, and RF > 1:40.

UAS7	N studied	Numbers (%)
Activity based on UAS7 28-42: severe	48	21 (43,7%)
16-27: moderate	48	7 (14,5%)
7-15: mild	48	15 (31,2%)
1-6: well-controlled	48	2 (4,1%)
0: itch-and wheals-free	48	3 (6,5 %)

Table 3:Weekly Urticaria Activity Score (UAS7) was recorded by the patients for seven consecutive days prior to sampling day. Patients were classified according UAS7 as follows: severe CSU (UAS7 = 28-42), moderate CSU (UAS7 = 16-27), mild CSU (UAS7 = 7-15), well-controlled CSU (UAS7 = 1-6) and itch-and wheals-free (UAS7 = 0).

Figures

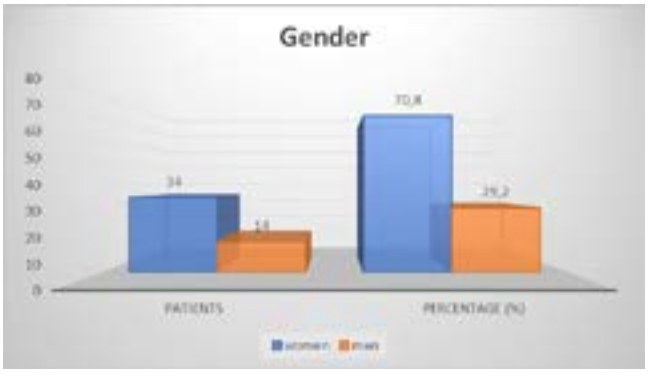

Figure 1: Number of patients (gender)

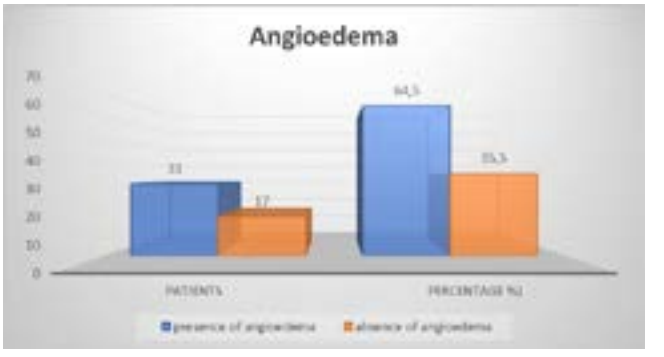

Figure 2: Presence of angioedema

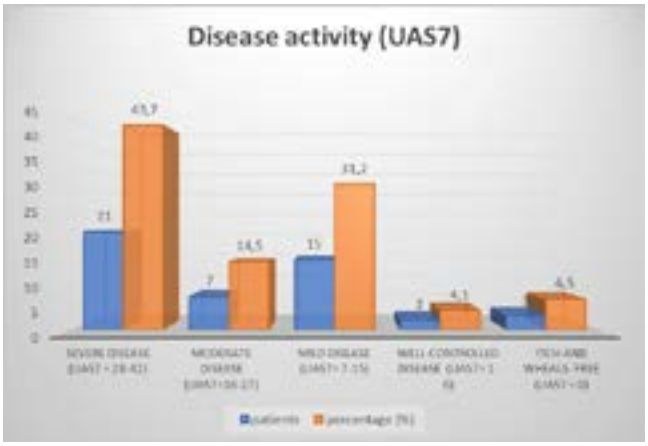

Figure 3: Disease activity (UAS7)

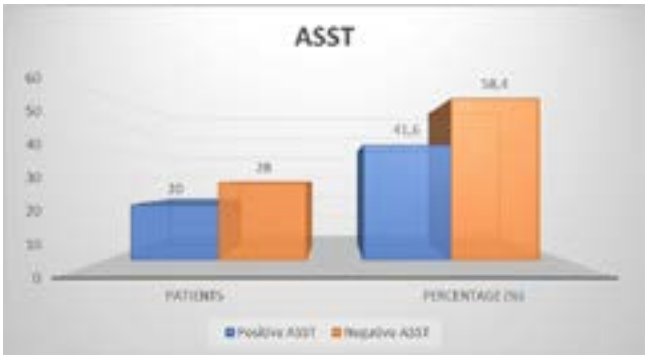

Figure 4: ASST

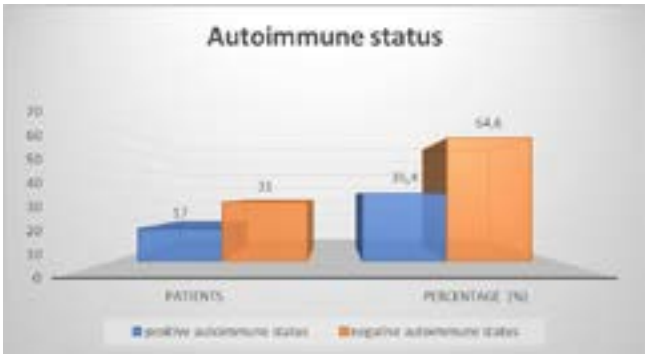

Figure 5: Autoimmune status

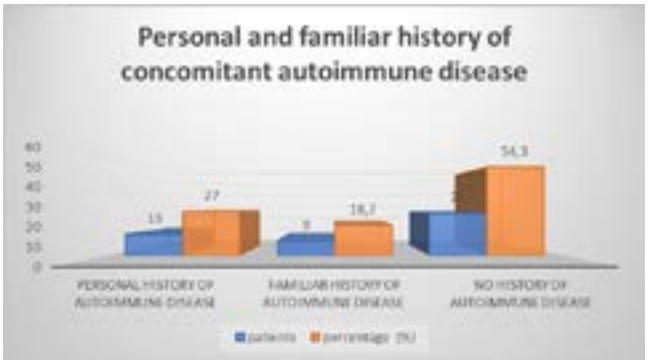

Figure 6: Personal and familiar history of concomitant autoimmune disease

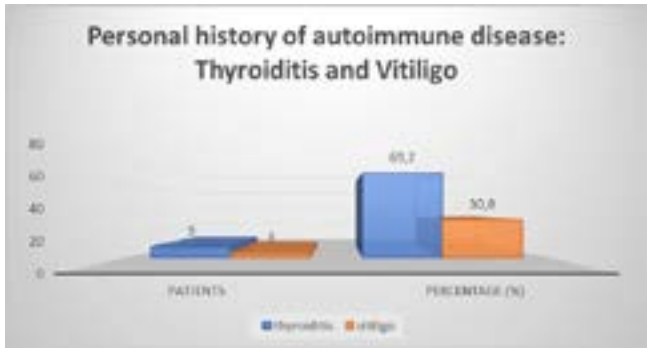

Figure 7: Personal history of autoimmune disease: Thyroiditis and Vitiligo

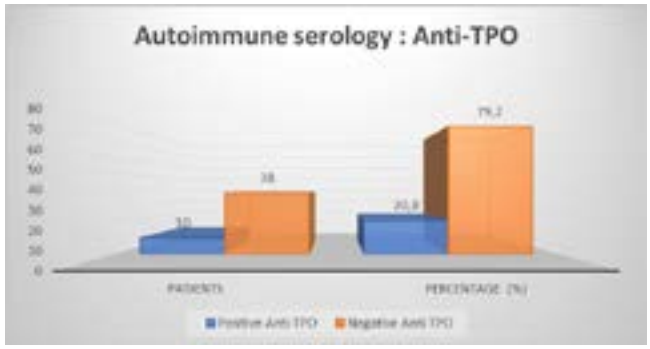

Figure 8: Autoimmune serology: Anti-TPO

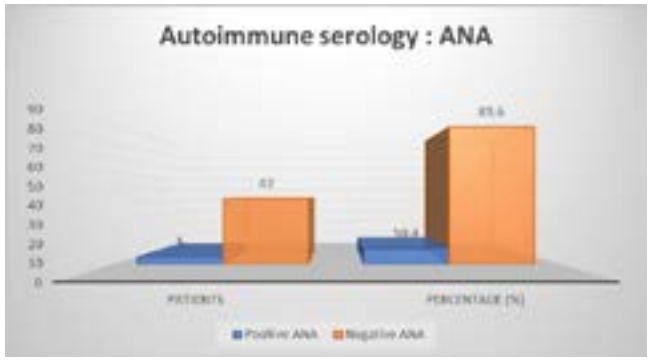

Figure 9: Autoimmune serology: ANA

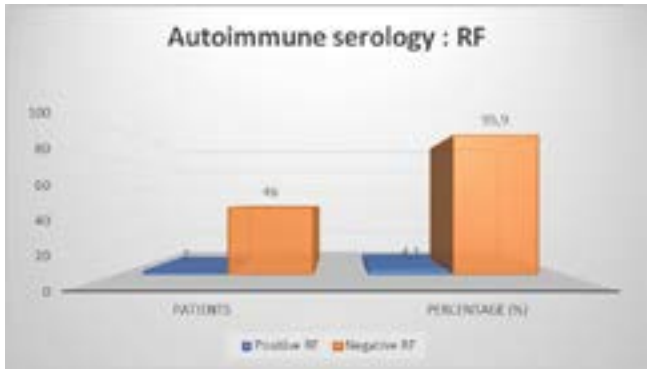

Figure 10: Autoimmune serology: RF

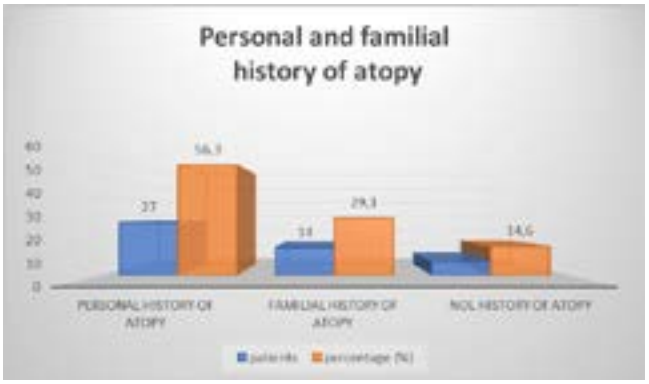

Figure 11: Personal and familiar history of atopy

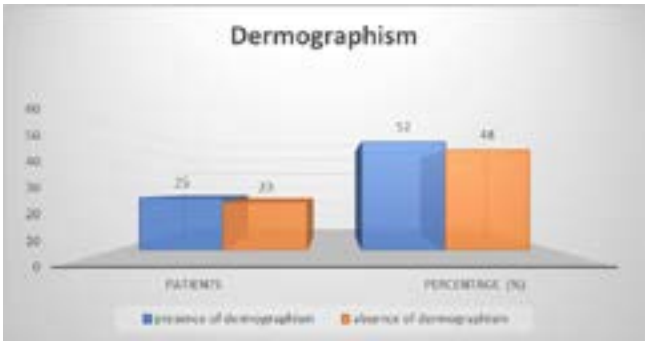

Figure 12: Personal and familiar history of dermographism

DISCUSSION

For more than 30 years, several lines of evidence argue for an auto- immune basis of CSU, or at least in a subgroup of them. In this study, we focused on associations of concomitant autoimmune disease and/or presence of AAbs (IgG-TPO, ANA and RF) and positivity of ASST. We found a relatively high incidence of autoimmune disorders and AAbs (autoimmune status) in patients with CSU. Onethird of the patients had concomitant autoimmune disease and/ or AAbs, mainly autoimmune thyroiditis. Moreover, a familial history of autoimmune disease was also found in 18,7% of patients. A positive wheal-and-flare reaction to ASST was found in 41,6 % of patients.

In a sentinel study conducted by Grattan et al., 12 patients with chronic urticaria were subjected to intradermal autologous serum injection (13). Seven of the 12 subjects (of whom six were female) mounted a positive wheal-and-flare reaction to this test, and fewer of these patients described a history of disease exacerbation with application of pressure when compared to patients with a negative injection test. Though theoretically performed by Grattan et al. (13), the autoimmune etiology of CSU was further supported by formal development of the autologous serum skin test (ASST), an in vivo assay of mast cell activation that is induced by intradermal injection of a patient's serum.Furthermore, the positivity of the test has been shown to persist even when CSU patients are in clinical remission, particularly in subjects with autoimmune thyroiditis (14).

An increased prevalence of clinical hypothyroidism (i.e., Hashimoto's thyroiditis) as well as hyperthyroidism has been found among patients with CSU, with one study estimating 23 times and seven times greater odds for hypothyroidism in female and male patients with chronic urticaria compared to control subjects, respectively (15). Patients with CSU also demonstrate higher levels of IgE anti-thyroid peroxidase (anti-TPO) antibodies relative to healthy controls, though this distribution was found to be bimodal with 39% of CSU patients exhibiting IgE anti-TPO levels similar to control subjects (IgE anti-TPOlow) (16). Autoallergic mast cell activation has been shown to occur in a variety of skin disorders including atopic dermatitis (16,17). Thyroid disease is the most commonly reported autoimmune condition in patients with CU. In the literature, the frequency of thyroid autoimmunity in patients with CU encompasses a vast range of values, varying from 6.5%(18) to 57%(19). In a recent large study of 12,778 CU patients by Cofino-Cohen et al.,(15) it was found that 9.8% of patients had hypothyroidism, compared with 0.6% in the control group. In the same study (15), anti-thyroid antibodies were significantly more common in CU patients than controls. Of the patients with CU who were clinically euthyroid, anti-thyroperoxidase antibodies were found in approximately 2.7% and antithyroglobulin antibodies were found in 0.6%.Treatment of concomitant thyroid disease was reported to induce remission of CU (20). Of patients with CU and hypothyroidism, RA was the most frequently identified additional autoimmune disease. The odds of having RA were 13.25 times higher in those with CU than in the control group (15). The major laboratory marker of RA, rheumatoid factor, was reported by Ryhal et al. to be significantly increased in patients with CU (21).

CONCLUSIONS

To conclude, in this prospective study, we found a relatively high incidence of concomitant autoimmune disease and AAbs. Onethird of the patients had concomitant autoimmune disease and/ or AAbs, mainly autoimmune thyroiditis. A positive wheal-and-flare reaction to ASST was found in more than one third of the patients. Almost

half of the patients had a personal history of atopy and presence of dermographism. Our study brings additional evidences over the utility of those clinical and biological parameters to be investigated in patients with CSU as they could be related to disease activity or autoimmunity.

REFERENCES

1. Zuberbier T., Balke M., Worm M. Epidemiology of urticaria: a representative cross-sectional population survey. ClinExp Dermatol. 2010;35:869–873.
2. Baiardini I., Giardini A., Pasquali M. Quality of life and patient's satisfaction in chronic urticaria and respiratory allergy. Allergy. 2003;58:621–623.
3. Kolkhir P., André F., Church M.K. Potential blood biomarkers in chronic spontaneous urticaria. ClinExp Allergy. 2017;47:19–36.
4. Ensina L.F., Cusato-Ensina A.P., Cardona R. Advances in the pathogenesis representing definite outcomes in chronic urticaria. CurrOpin Allergy Clin Immunol. 2019;19:193–197.
5. Ferrer M., Boccon-Gibod I., Gonc¸alo M. Expert opinion: defining response to omalizumab in patients with chronic spontaneous urticaria. Eur J Dermatol. 2017;27:455–463.
6. Kolkhir P, Church MK, Weller K, Metz M, Schmetzer O, Maurer M. Autoimmune chronic spontaneous urticaria: What we know and what we do not know. J Allergy Clin Immunol. 2017 Jun;139(6):1772-1781.e1. doi: 10.1016/j.jaci.2016.08.050. Epub 2016 Oct 21. PMID: 27777182.
7. Chronic urticaria and autoimmunity: associations found in a large population study.
1. Confino-Cohen R, Chodick G, Shalev V, Leshno M, Kimhi O, Goldberg A
2. J Allergy Clin Immunol. 2012 May; 129(5):1307-13.
8. Baumann K, Marcelino J, Skov PS, Santos MCP, Wyroslak I, Scheffel J, Altrichter S, Woetmann A, Costa C, Maurer M. Autologous serum skin test reactions in chronic spontaneous urticaria differ from heterologous cell reactions. J EurAcad Dermatol Venereol. 2021 Jun;35(6):1338-1345. doi: 10.1111/jdv.17131. Epub 2021 Mar 2. PMID: 33475206.
9. Gonzalez-Diaz SN, Sanchez-Borges M, Rangel-Gonzalez DM, Guzman-Avilan RI, Canseco-Villarreal JI, Arias-Cruz A. Chronic urticaria and thyroid pathology. World Allergy Organ J. 2020 Mar 6;13(3):100101. doi: 10.1016/j.waojou.2020.100101. PMID: 32180891; PMCID: PMC7063156.
10. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA(2) LEN/ EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. Allergy 2014;69(7):868-87.
11. Khalil S, McBride D, Gimenez-Arnau A, Grattan C, Balp M, Stull D. Weekly Urticaria Activity Score (UAS7) and Dermatology Life Quality Index (DLQI) in Validation of Chronic Spontaneous/ Idiopathic Urticaria (CSU/CIU) Health States. Annual Scientific Meeting of the American Academy of Allergy, Asthma &Immu- nology; Houston, Texas, USA 2015.
12. Konstantinou GN, Asero R, Maurer M, Sabroe RA, Schmid-Gren- delmeier P, Grattan CEH. EAACI/GA2LEN task force consen- sus report: the autologous serum skin test in urticaria. Allergy 2009;64(9):1256-68.
13. Grattan CE, Wallington TB, Warin RP, Kennedy CT, Bradfield JW. A serological mediator in chronic idiopathic urticaria–a clinical, immunological and histological evaluation. Br J Dermatol. (1986) 114:583–590. doi: 10.1111/j.1365-2133.1986.tb04065.x
14. Fusari A, Colangelo C, Bonifazi F, Antonicelli L. The autologous serum skin test in the follow-up of patients with chronic urticaria. Allergy. (2005) 60:256–8. doi: 10.1111/j.1398-9995.2005.00673.x
15. Confino-Cohen R, Chodick G, Shalev V, Leshno M, Kimhi O, Goldberg A. Chronic urticaria and autoimmunity: associations found in a large population study. J Allergy Clin Immunol.(2012) 129:1307–13. doi: 10.1016/j.jaci.2012.01.043
16. Altrichter S, Peter HJ, Pisarevskaja D, Metz M, Martus P, Maurer M. IgE mediated autoallergy against thyroid peroxidase–a novel pathomechanism of chronic spontaneous urticaria? PLoS ONE. (2011) 6:e14794. doi: 10.1371/journal.pone.0014794
17. Valenta R, Duchêne M, Pettenburger K, Sillaber C, Valent P, Bettelheim P, et al. Identification of profilin as a novel pollen allergen; IgE autoreactivity in sensitized individuals. Science.(1991) 253:557–60. doi: 10.1126/science.1857985
18. Thyroid disease is the most commonly reported autoimmune condition in patients with CU. In the literature, the frequency of thyroid autoimmunity in patients with CU encompasses a vast range of values, varying from 6.5%24 to 57%25
19. Aamir IS, Tauheed S, Majid F, et al. Frequency of autoimmune thyroid disease in chronic urticaria. J Coll Physicians Surg Pak. 2010 Mar;20(3):158-61.

20. Bangash SA, Bahna SL. Resolution of chronic urticaria and angioedema with thyroxine. Allergy Asthma Proc. 2005 Sep-Oct;26(5):415-7.
21. Ryhal B, DeMera RS, Shoenfeld Y, et al. Are autoantibodies present in patients with subacute and chronic urticaria? J InvestigAllergol Clin Immunol. 2001;11(1):16-20.