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DIAGNOSIS AND TREATMENT OF CHRONIC URTICARIA: THE IMPORTANCE OF AUTOIMMUNE ASPECTS AND COMORBIDITY

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Abstract . The study **aimed** to conduct a comprehensive systematic review of the literature on the autoimmune mechanisms associated with chronic spontaneous urticaria (CSU) in adults, explore the association between chronic urticaria (CU) and autoimmune disorders, analyze two case reports, and develop a diagnostic algorithm considering the autoimmune pathogenesis.

Materials and Methods. The literature review was conducted to study the mechanisms underlying autoimmune CU. Two case reports were analyzed and a diagnostic algorithm for patients suspected of autoimmune urticaria was formulated.

Results. CU significantly impairs patients' quality of life, posing problems in daily activities and is often associated with concomitant autoimmune diseases. Though the pathogenesis of CSU remains incompletely understood, in recent years, there has been significant progress in understanding the pathophysiology of this condition, prompting researchers to explore new agents, especially biological ones, in cases with severe refractory urticaria. We have developed a diagnostic algorithm aimed at improving the management tactics for CSU and autoimmune pathology, that involves a thorough collection of complaints, medical history, performing a series of basic laboratory tests for specific markers of autoimmune disorders, and expanding their spectrum with detailed differential diagnostics.

Conclusions. CU is an important medical and social issue that requires an interdisciplinary personalized approach to patients. The diagnosis of the condition involves a comprehensive approach, considering potential concomitant autoimmune disorders and detailed laboratory investigations, especially in cases refractory to standard second-generation antihistamine therapy. The treatment of CU, specifically the stepwise therapy protocol based on symptom severity and response to treatment and aimed at reducing symptoms, improving patients' quality of life, and achieving CU remission, is outlined in various national and international guidelines, and is carried out gradually, involving three lines of therapy.

Keywords: Chronic Urticaria; Autoimmune Thyroiditis; Systemic Lupus Erythematosus.

Introduction

In recent years, there has been an increase in the prevalence of allergic diseases associated with adverse environmental and genetic factors, and a range of epigenetic influences. Family physicians and allergists pay special attention to chronic urticaria (CU) characterized by recurrent migrating skin lesions, called wheals or hives and/or angioedema (AE) lasting more than six weeks [9,13].

It is worth noting that in patients with urticaria, wheals have three characteristic features: sharply circumscribed superficial swelling of varying sizes and shapes, almost invariably surrounded by reflex erythema, an itching or sometimes burning sensation, a fleeting nature, with the skin returning to its normal appearance usually within 30 min to 24 h, and a resolution without residual manifestations. AE is characterized by a sudden, pronounced erythematous or skin-colored swelling of the deep dermal layers, subcutaneous tissue, and mucous membranes, tingling, and sometimes pain rather than itch, with a slower resolution compared to wheals (up to 72 h).

Based on the absence/presence of specific triggers, CU may be spontaneous or inducible. Chronic spontaneous urticaria (CSU) is characterized by the unpredictable appearance of wheals and/or AE for more than six weeks due to known (autoreactivity) or unknown reasons, significantly impacting patients' quality of life (QoL) [9].

CSU is a predominant form of CU, which can present with daily signs and symptoms or an intermittent/recurring course. It can relapse after months or even years of complete remission (5-10 years). Such patients are recommended to undergo a reassessment of the necessity for continuing or opting for alternative medication treatment every 3-6 months as the severity of urticaria can vary, and spontaneous remission can occur at any time.

Predictors for a more prolonged course of CSU include high total immunoglobulin E (IgE) levels, AE, concomitant chronic induced urticaria, severe disease presentation, and autoreactivity proven by the autologous serum skin test (ASST). The autoimmune processes play a significant role in the mechanisms underlying the

development of CSU. CSU patients are often diagnosed with other autoimmune diseases, including systemic connective tissue disorders and autoimmune thyroid disease [3,10]. Therefore, ongoing research focuses on the pathogenetic aspects of CSU, specifically thyroid, nuclear, and other autoantigens that bind to autoreactive IgE. Furthermore, emphasis is placed on understanding the interaction among diverse factors involved in the pathogenesis of CU [1]. It is worth noting that several circulating mediators, specifically pro-inflammatory cytokines such as interleukin-1β (IL-1β), IL-6, IL-10, IL-17, and tumor necrosis factor alpha (TNFα), could potentially play an indirect role in the activation of mast cells in CSU [10].

The immunopathogenesis of CSU encompasses two types: Type I CSU mediated by IgE autoantibodies to autoantigens, often linked with elevated C-reactive protein (CRP) levels and Type IIb autoimmune CSU mediated by autoantibodies that activate mast cells, characterized by IgE autoantibodies to autoantigens, reduced basophil and eosinophil levels, low total IgE levels, and elevated IgG-anti-thyroid peroxidase (TPO) levels. It is important to note that a high ratio of IgG-anti-TPO to total IgE is the best surrogate marker for Type IIb autoimmune CSU. The ASST can help demonstrate the autoimmune nature of CSU.

CU is often associated with an autoimmune condition and can be the initial clinical manifestation of several autoimmune pathologies, including systemic lupus erythematosus (SLE), autoimmune thyroiditis, urticarial vasculitis, Sjögren's syndrome, etc. Therefore, it is imperative for family physicians, allergists, immunologists, dermatologists, rheumatologists, and endocrinologists to make a differential diagnosis to distinguish between systemic connective tissue disorders, inherited and acquired immunodeficiencies, and urticarial vasculitis, and in cases involving periodic swelling, differentiate CU from hereditary AE.

The important goals of examining patients with CSU are to confirm the diagnosis; to exclude differential diagnosis; to identify the underlying causes of the disease, conditions that may impact disease activity, comorbidities, and complications of CSU. Furthermore, there is a need for evaluating predictors of CSU severity, assessing its impact on QoL, analyzing treatment responses, as well as monitoring disease activity to ensure complete disease control.

Recurrent urticaria episodes persisting from several months to several years should raise the suspicion of underlying immunodeficiency and autoinflammatory syndromes. In these cases, CU is often accompanied by additional inflammatory symptoms such as fever, arthritis, myalgia, serositis, hepatosplenomegaly, eye involvement, and/or neurological disorders.

The diagnosis and management of a patient with CSU primarily involves an accurate medical history, physical examination, and routine (recommended) investigations, including complete blood count (CBC) with differential, erythrocyte sedimentation rate (ESR) and/or serum C-reactive protein (CRP) levels, and IgG-anti-TPO and total IgE levels. Subsequently, an allergist/immunologist selects specific examinations tailored to the type and subtype of urticaria and determines the necessity of consultations with other specialists.

For further assessment and monitoring of disease activity in patients with CSU, the Urticaria Activity Score (UAS7) and Angioedema Activity Score (AAS) are used. Additionally, there are mobile applications tracking daily symptoms related to the condition.

When diagnosing CSU, it is necessary to minimize or reduce exposure to physical triggers, certain foods, contact substances, emotional stressors, and certain medications, notably nonsteroidal anti-inflammatory drugs (NSAIDs) and angiotensin-converting enzyme (ACE) inhibitors. Moreover, comorbid infections caused by Helicobacter pylori, urinary tract infections, parasite invasions, dental, or gynecological infections necessitate treatment. Other comorbid conditions such as autoimmune thyroid disease, arterial hypertension, and metabolic syndrome should be treated as well [13].

The treatment of CU, specifically the stepwise therapy protocol based on symptom severity and treatment response, has been described in various national and international guidelines [14] and provides for a stepwise approach to medication prescription. First-line treatment includes second-generation antihistamines (sgAHs) at standard doses, with the possibility of increasing the dosage up to fourfold [6,8]. When combining AHs, no positive therapeutic effect was noted compared to increasing the dosage of a single non-sedating antihistamines (NSAH) [14]. In some cases, where CU coincided with AE, a combination of leukotriene receptor antagonists and sgAHs showed favorable outcomes [7].

Nevertheless, despite standard AH doses, some patients experience uncontrolled symptoms without positive therapeutic effects upon increasing the dosage. In such cases, second-line therapy is recommended, involving the additional prescription of omalizumab which is a recombinant humanized monoclonal antibody that binds to circulating IgE and reduces the release of inflammatory mediators from mast cells and basophils. Omalizumab is the only licensed medication for treating CU in patients unresponsive to sgAH therapy [8].

Multiple biological agents aimed at treating refractory CU are currently being researched worldwide, including ligelizumab, rituximab, dupilumab, secukinumab, TNFα inhibitors, fenebrutinib, remibrutinib, tezepelumab, etc. [7,8].

Third-line therapy is administered in severe cases of CU, when the combination of high doses of sgAHs and omalizumab proves ineffective, and involves cyclosporine A. This agent, however, cannot be recommended as standard treatment due to high frequency of side effects. Studies have suggested that cyclosporine A presents much better risk/benefit ratio compared to glucocorticoids [5,8].

It is noteworthy that urticaria can manifest as a symptom of autoimmune diseases or can develop in individuals with an already confirmed diagnosis. SLE typically manifests with skin and mucous membrane changes, specifically a distinctive butterfly-shaped erythema on the cheeks and the bridge of the nose, which can also appear on the periorbital forehead, neck, and décolleté during the periods of increased disease activity, photosensitivity, oral and nasal mucosal lesions, and skin changes such as urticarial non-itchy lesions typically persisting for more than 24 h [11].

However, in recent years, there has been a trend towards atypical clinical course and manifestations of some autoimmune diseases, that is crucial for allergists, immunologists, rheumatologists, and dermatologists.

Case Report No. 1

A 42-year-old female presented to a family physician with complaints of rashes on the face, arms, and legs, periorbital edema, lip swelling, sudden fatigue, and generalized weakness. A five-day course of AHs showed no positive results. She was referred to an allergist for further examination and treatment. Upon detailed questioning, the patient reported that facial rash occurred approximately a year ago but disappeared after taking a few AHs. Throughout the year, intermittent manifestations of the rash on the arms, legs, and face were noted, recurring periodically and then disappearing. This exacerbation occurred after a seaside vacation where the patient consumed exotic fruits and seafood. Additionally, the patient noted hair loss over the past few months. The allergist prescribed a series of examinations, including CBC, biochemical profile, CRP test, total IgE test, abdominal ultrasonography (US), stool ova and parasite test, antibody serology test, and food allergy test.

CBC showed mild leucopenia ($3.1x10^9$/L), thrombocytopenia ($138x10^9$/L), and raised ESR - 21 mm/h. Biochemical profile revealed an increase in CRP levels up to 1.98 mg/dL and creatinine level of 106.5 μmol/L. Total IgE level was found to be 159.94 IU/mL.

Abdominal US showed a cystic formation in the spleen and bilateral nephroptosis. Knee US revealed signs of osteoarthritis and chronic synovitis in both knee joints. No evidence of helminthic invasion was found.

The IgE comprehensive food allergy test demonstrated primary sensitization to molluscan shellfish allergens.

As the treatment of urticaria was ineffective with blood tests showing inflammatory changes, the patient underwent the antinuclear antibody (ANA) test for diagnosing systemic connective tissue diseases, with an antibody titer of 1:160 (positive test result). Afterward, the patient was referred to a rheumatologist, tested for specific autoantibodies to double-stranded deoxyribonucleic acid (anti-dsDNA) showing a value of 17 IU/ml, with a normal range up to 10 IU/ml, and screened for antiphospholipid syndrome, with the detection of lupus anticoagulant, IgM and IgG phospholipids, and IgM and IgG cardiolipins (all parameters were within normal ranges). Subsequently, all symptoms were thoroughly analyzed, including skin rashes on the face, arms, and legs, hair loss, time of their appearance (following sun exposure suggesting potential photosensitivity), test changes, and ANA presence. This led to a definitive diagnosis of chronic SLE in its active phase, characterized by skin manifestations (photosensitivity, urticaria, alopecia), joint involvement (bilateral knee osteoarthritis Rtg I-II indicating mild joint impairment), hematologic disorders (leukopenia, thrombocytopenia), and immunological phenomena (elevated Anti-dsDNA), with moderate activity (the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score of 8).

Upon analyzing the clinical case, urticaria and alopecia were the initial (manifest) signs of the systemic autoimmune process, followed by photosensitivity.

In cases where SLE is suspected, it is crucial to conduct testing for ANA by the indirect immunofluorescence assay (IIFA) on HEp-2 cells, with a titer ≥ 1:80 (or an equivalent test), as part of the diagnostic process. The next step is to sum up the scores obtained by identifying relevant clinical and laboratory symptoms. All classification criteria are organized into seven clinical domains and three immunological domains. Most domains include several SLE symptoms, each assigned a specific numerical value (score) based on the clinical significance of that symptom [12].

There are clinical and immunological diagnostic criteria for SLE (EULAR/ACR, 2022). Immunological domains include antiphospholipid antibodies (anticardiolipin or anti-β2-glycoprotein 1 (anti-β2GP1) antibodies, or lupus anticoagulant), complement system indicators (decreased C3 or C4 levels), and SLE-specific antibodies (antibodies to anti-dsDNA or anti-Smith antibodies).

Taking the above into account, the following diagnostic algorithm can be proposed for patients with CSU who are suspected of having SLE.

1. SLE is suspected in a patient diagnosed with CSU and presenting with individual lesions persisting for more than 24 h, photosensitivity, absence of itching, unresponsiveness to sgAHs, and two or more symptoms encompassing musculoskeletal constitutional disorders, skin lesions, reticuloendothelial disorders, hematologic disorders, alopecia, alongside renal, gastrointestinal, pulmonary, cardiovascular, and psychoneurological manifestations.
2. The ANA test is positive (≥1:80) and changes in laboratory parameters indicate anemia, thrombocytopenia, leucopenia, proteinuria (microalbuminuria).
3. The patient is referred to a rheumatologist to confirm diagnosis and determine disease activity - testing for autoantibodies to anti-dsDNA, screening for antiphospholipid syndrome, decreased complement C3 or C4 levels.
4. A mobile rheumatology assistant RheumaHelper (Slovenia) is recommended to confirm diagnosis and determine SLE activity.
5. High titers of SLE-specific antibodies, meeting ≥4 SLICC criteria or the 2022 ACR/EULAR classification criteria threshold score of 10 confirm the diagnosis of SLE.

Case Report No. 2

A 35-year-old female presented to an allergist with complaints of periodic rashes, itching, and fatigue. According to her medical history, these symptoms occurred periodically for the last six months, with the latest exacerbation lasting about a week.

The patient was prescribed the following examinations: CBC, biochemical profile, abdominal US, stool ova and parasite test, antibody serology test.

CBC showed high white blood cell count ($11.54x10^9$/L), high neutrophils ($9.42x10^9$/L), and high eosinophil count (8%). Biochemical profile revealed no abnormalities. The enzyme-linked immunosorbent assay (ELISA) for human immunodeficiency virus (HIV) was negative. The Wassermann reaction (WR) for syphilis was negative as well. Chest X-ray showed no lung and heart abnormalities.

Abdominal US showed signs of chronic acalculous cholecystitis.

The stool ova and parasite test yielded negative results. However, the levels of parasite-specific IgG antibodies indicated signs of giardiasis, with an index of 8.2, detected in the anti-Toxocara, anti-Ascaris, anti-Giardia, and anti-helminth IgG antibodies.

After consulting an infectious disease specialist and considering the test results, the patient was proposed a treatment regimen comprising a seven-day course of antiparasitic therapy and sgAHs at standard dose of one tablet a day.

After the course of treatment, the patient's general condition improved; however, it was a short-term remission, necessitating a more thorough re-examination and treatment adjustment.

CU can manifest as systemic connective tissue disorder and is often associated with other autoimmune disorders; therefore, the patient was tested for serum autoimmunity markers (autoimmune disorder panel). The results showed no specific autoimmunity markers. Thyroid US demonstrated changes in thyroid structure, specifically a diffuse reduction in thyroid echogenicity and increased vascularity, which are indicative of autoimmune thyroiditis. The subsequent evaluation involved assessing thyroid function through chemiluminescent immunoassay. Results indicated a serum concentration of 9.8 μIU/mL for thyroid stimulating hormone (TSH), a titer of 0.32 IU/L for TSH receptor antibody (TSHR-Ab), and 416.0 IU/mL for antibodies to TPO. Furthermore, the microparticle-based immunochromatographic test determined serum concentrations of free thyroxine (FT4) and free triiodothyronine (FT3) as 1.4 ng/dL and 2.8 pg/mL, respectively. The patient was diagnosed with autoimmune thyroiditis and subclinical hypothyroidism. The treatment aimed at correcting thyroid function was prescribed. It included levothyroxine at a dose of 75 mcg/day with subsequent monitoring of hormone levels, antibodies, and a review of prescriptions. Additionally, the patient was recommended to consult a surgeon regarding cholecystectomy.

Therefore, it is imperative to acknowledge that in patients with a complex family history, CSU, inadequate responsiveness to standard doses of sgAHs, antithyroid antibodies (anti-microsomal, anti-thyroglobulin (anti-TG), and anti-TPO) as well as thyroid hormone levels should be assessed. As up to 57.4% of CSU patients present with autoimmune thyroid disease, research on the relationship between CSU and autoimmune thyroid disorders continues [2].

Thus, examining patients with CSU is a lengthy process that requires step-by-step clinical thinking and involves confirming the diagnosis, ruling out differential diagnoses, identifying the primary causes of the condition, factors affecting disease activity, comorbidities, consequences of CSU, assessing predictors of disease severity and treatment response as well as monitoring CSU activity and its impact on QoL and disease control.

CSU poses a challenge to internal medicine necessitating an interdisciplinary approach, especially in patients with a comorbidity. A modern approach to patient management requires integrating scientific evidence and the experience of practicing healthcare professionals and individuals affected by the condition.

To improve the management approach to CSU and autoimmune pathology, we have developed a diagnostic algorithm and further care plan for these patients.

1. Verification of CSU diagnosis in an individual with symptoms persisting for more than 6 months requires accurate complaint and history collection, identification of potential triggers, analysis of the frequency and circumstances of rash occurrence, physical examination, itch assessment, photographs of past skin lesions, previous treatment outcomes, and AH effectiveness.

2. The next step is to discuss the diagnostic plan (basic laboratory tests) and CSU treatment with the patient, considering their comorbidities. In cases requiring differential diagnosis, an interdisciplinary collaboration should be established.

3. Prescription of stepwise CSU therapy with a subsequent assessment of treatment effectiveness (UAS7, mobile applications) 2-4 weeks after the start of treatment or earlier if symptoms are intolerable for therapy escalation/de-escalation and excluding alternative diagnoses, alongside the addition of omalizumab 6 months post-treatment initiation or earlier, and scheduling follow-ups for patients achieving complete disease control and minimal medication load (UAS7=0) every 12 months.

4. The inclusion of additional diagnostic tests such as ANA, anti-dsDNA, IgG-anti-TPO, and interdisciplinary collaboration becomes imperative if a patient presents with recurrent fever, alopecia, photosensitivity, joint syndrome, wheals persisting for more than 24 h, polymorphic rash, pigmentation/hypopigmentation areas, excoriations, and unresponsiveness to treatment.

It should be noted that promising medications and potential targets in CU are currently being researched [4]. In the near future, new biological agents and small molecules currently under study will be used for managing severe and refractory forms of CU.

Conclusions

1. CU is a multifactorial condition that requires an interdisciplinary personalized approach to patients, considering potential triggers, medical history, previous treatment effectiveness, and patient's QoL.

2. The strategy for diagnosing CU involves a comprehensive approach, including a thorough collection of symptoms, medical history, photographic evidence, performing basic laboratory tests, followed by a broader spectrum of tests, and detailed differential diagnosis.

3. In cases of CSU accompanied by hyperthermia, arthralgia, myalgia, absence of itching, persistence of individual rash elements for more than 24 h, alopecia, photosensitivity, and unresponsiveness to AHs, seeking consultation with other medical specialists such as rheumatologists, endocrinologists, and immunologists, is crucial for determining further management strategies.

4. The general treatment plan for CU is stepwise (gradual). The starting point and progression between steps depend on the clinical course, individual response to therapy, and disease monitoring.

Informed Consent

All patients provided informed consent for the use of their data and examination results, and publication of materials.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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References

1. Bansal CJ, Bansal AS. Stress, pseudoallergens, autoimmunity, infection and inflammation in chronic spontaneous urticaria. Allergy Asthma Clin Immunol. 2019;15:56. Available from: https://doi.org/10.1186/s13223-019-0372-z

2. 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;13(3):100101. Available from: https://doi.org/10.1016/j.waojou.2020.100101

3. Kaplan A, Lebwohl M, Giménez-Arnau AM, Hide M, Armstrong AW, Maurer M. Chronic spontaneous urticaria: Focus on pathophysiology to unlock treatment advances. Allergy. 2023;78(2):389-401. Available from: https://doi.org/10.1111/all.15603

4. Kolkhir P, Altrichter S, Munoz M, Hawro T, Maurer M. New treatments for chronic urticaria. Ann Allergy Asthma Immunol. 2020;124(1):2-12. Available from: https://doi.org/10.1016/j.anai.2019.08.014

5. Melchers S, Nicolay JP. Chronic spontaneous urticaria - status quo and future. Allergo J Int. 2023;32:326-36. Available from: https://doi.org/10.1007/s40629-023-00272-7

6. Podder I, Dhabal A, Chakraborty SS. Efficacy and safety of up-dosed second-generation antihistamines in uncontrolled chronic spontaneous urticaria: a review. J Clin Aesthet Dermatol. 2023;16(3):44-50.

7. Yosipovitch G, Soares GB, Mahmoud O. Current and Emerging Therapies for Chronic Spontaneous Urticaria: A Narrative Review. Dermatol Ther (Heidelb). 2023;13(8):1647-60. Available from: https://doi.org/10.1007/s13555-023-00972-6

8. Zuberbier T, Bernstein JA, Maurer M. Chronic spontaneous urticaria guidelines: what is new? J Allergy Clin Immunol. 2022;150(6):1249-55. Available from: https://doi.org/10.1016/j.jaci.2022.10.004

9. Bondarenko TM, Nazar OV, Babadzhan VD. Angioedema. Difficult patient. Klinichna immunolohiia. Alerholohiia. Infektolohiia. 2023;2:6-9.

10. Okhotnikova OM, Romanchuk AA, Grishchenko OM. Chronic urticaria and inflammatory bowel disease - is it worth looking further? Modern Pediatrics. Ukraine. 2021;6(118):55-60. Available from: https://doi.org/10.15574/SP.2021.118.55

11. Protsenko GO, Dubas VV, Uzun SV, Tsokalo YV, Zbarashchenko-Hasan MI. Skin manifestation of systemic lupus erythematosus (case from clinical practice). Journal of Rheumatology. 2023;91(1):1-6. Available from: https://doi.org/10.32471/rheumatology.2707-6970.91.17654

12. Rishko MV, Prylypko LB, Kedyk AV, Lazur YaV. Diahnostychni kryterii revmatychnykh zakhvoriuvan. Metodychni rekomendatsii dlia studentiv starshykh kursiv, likariv zahalnoii praktyky-simeinoii medytsyny, likariv-terapevtiv, likariv-revmatolohiv pid redaktsiieiu Rishka MV. c2002. 39p.

13. Sanchez-Borgesa M, Ansotegui IJ, Baiardini I, Bernstein J, Canonica GW, Ebisawa M, et al. The challenges of chronic urticaria part 1: Epidemiology, immunopathogenesis, comorbidities, quality of life, and management. World Allergy Organ J. 2021;14(6):100533. Available from: https://doi.org/10.1016/j.waojou.2021.100533

14. Sanchez-Borgesa M, Ansotegui IJ, Baiardini I, Bernstein J, Canonica GW, Ebisawa M, et al. The challenges of chronic urticaria part 2: Pharmacological treatment, chronic inducible urticaria, urticaria in special situations. World Allergy Organ J. 2021;14(6):100546. Available from: https://doi.org/10.1016/j.waojou.2021.100546

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