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Editorial

Screening for Autoimmune Comorbidities in Patients With Chronic Spontaneous Urticaria: Which Tests to Whom

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▸ See the article "Autoimmune Diseases Are Linked to Type IIb Autoimmune Chronic Spontaneous Urticaria" in volume 13 on page 545.

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Chronic spontaneous urticaria (CSU) is a common skin disease defined as recurrent itchy wheals, angioedema or both lasting longer than 6 weeks without identifiable external triggers. Mast-cell activation and degranulation are an essential pathway to evoke wheal and angioedema in various types of urticaria.[1] Although many non-immunological factors, including complements, neuropeptides and host defense peptides, have been found to affect mast-cell function, up to 50% of patients with CSU have autoimmune disorders: type I autoallergy (immunoglobulin [Ig] E autoantibodies) and type IIb autoimmune reactions (IgG autoantibodies).[2]

Accumulating evidence suggests strong associations between CSU and various autoimmune diseases.[3-7] In the general population, the prevalence of autoimmune diseases is estimated at 4.5%, prevailing in females (6.4% vs. 2.7%),[8] whereas the prevalence of individual autoimmune diseases are less than 1%. A recent systematic literature review showed that autoimmune diseases with relatively high prevalence in the general population, such as autoimmune thyroid disease, pernicious anemia, vitiligo, celiac disease, type I diabetes and rheumatoid arthritis, are also quite common in CSU patients.[3] Thyroid diseases are the most frequently reported autoimmune diseases accompanying CSU globally.[4,5,7] Within 10 years after the diagnosis of chronic urticaria, most of the autoimmune comorbidities have been detected. In addition, Kim *et al.*[6] reported that patients having autoimmune thyroid disease were at higher risk of developing CSU with a hazard ratio of 1.46. Female sex and atopic diseases, including allergic rhinitis, asthma and atopic dermatitis, were determined as significant risk factors of CSU in patients with autoimmune thyroid disease.[4,6] However, prior epidemiological studies have not shown how accompanying autoimmune diseases affect the severity and prognosis of CSU. Also, it is not known which types of CSU are likely to have an autoimmune disease and which tests should be performed for their diagnoses.

In the current issue of the *Allergy, Asthma and Immunology Research*, Kolkhir *et al.*[9] reported that, of 1,199 CSU patients, 28% had autoimmune comorbidities—mostly autoimmune thyroid diseases (25.4%), vitiligo (2.3%) and rheumatoid arthritis (1.0%)—and 2% had more than 2 autoimmune diseases. In patients with CSU, autoimmune comorbidities were found to be associated with age over 40 years, female sex and the presence of family history of autoimmune diseases or angioedema, and higher disease activity. Laboratory features of CSU patients with autoimmune comorbidities included low total IgE levels as well as low blood eosinophil and

basophil counts, whereas the positivity for IgG against FcεRIα did not differ according to the presence of autoimmune diseases. One of the strengths of this study is that they specified autoimmune CSU based on the results of 3 tests: autologous serum skin test (ASST), basophil histamine release assay (BHRA) and basophil activation test (BAT) as well as compared the prevalence of autoimmune comorbidities and patient characteristics according to this type IIb autoimmune CSU. All the 3 tests were found to be useful for detecting accompanying autoimmune diseases; however, BAT and BHRA, which are functional tests, were confirmed to be more sensitive than ASST. Moreover, type IIb autoimmune CSU showed a significant association with non-response to omalizumab, similar to the presence of antinuclear antibody/IgG autoantibody against thyroid peroxidase (TPO) reflecting autoimmunity.

The urticaria guidelines recommend the evaluation of thyroid hormones and autoantibodies at the extended diagnostic stage only for long-lasting chronic urticaria and suspected medical history.[1,10] Kolkhir *et al.*[9] found that 24% of CSU patients even with normal thyroid-stimulating hormone levels had autoimmune diseases. However, the positivity for IgG anti-TPO is observed in 90% of autoimmune thyroid diseases[11] and plays a role in progressing overt hypothyroidism[12] and in predicting poor response to omalizumab treatment in CSU patients.[9] Therefore, they suggest that all adult CSU patients should be checked for IgG anti-TPO and symptoms of autoimmune diseases at the initial diagnostic workup. In patients positive for IgG anti-TPO, they recommend tests for thyroid function and autoimmune CSU. Further studies on how IgG anti-TPO is involved in CSU pathogenesis can help develop new therapeutics effective in autoimmune CSU.

In conclusion, autoimmune thyroid disease is one of the most common autoimmune comorbidities in CSU patients and is associated with type IIb autoimmune characteristics, higher UAS7, the presence of angioedema and non-response to omalizumab. Deciphering the genetic basis of CSU along with IgG anti-TPO and type IIb autoimmunity screening will contribute to implementing precision medicine in CSU.

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