

Graves Disease Associated With Chronic Idiopathic Urticaria: 2 Case Reports

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■ Abstract

Chronic idiopathic urticaria (CIU) is well known to be associated with antithyroid peroxidase antibodies and autoimmune thyroiditis. Coexisting Graves disease has only rarely been observed. We describe 2 patients with CIU who developed autoimmune hyperthyroidism with antithyrotropin receptor antibodies. Antithyroid peroxidase antibodies were also present in 1 of the patients, but both responded poorly to high-dose antihistamine therapy. Both patients improved significantly, and their thyroid function recovered with carbimazole. We advise clinicians to be alert to the symptoms of hyperthyroidism when patients with CIU respond poorly to antihistamine therapy, as prompt treatment of hyperthyroidism significantly improves urticaria.

Key words: Chronic urticaria. Graves disease.

■ Resumen

Es bien conocido que la urticaria crónica idopática (UCI) se asocia con anticuerpos antiperoxidasa y tiroiditis autoinmune. La asociación con la enfermedad de Graves solamente se ha observado en raras ocasiones. Describimos 2 pacientes con UCI que desarrollaron hipertiroidismo autoinmune con anticuerpos anti-receptor de tirotrópina. Además, un paciente presentaba anticuerpos antiperoxidasa tiroidea, pero los dos respondieron pobremente al tratamiento con antihistamínicos a dosis elevadas. Los dos pacientes mejoraron significativamente, y su función tiroidea se recuperó con carbamazol. Aconsejamos a los clínicos que estén alerta a los síntomas de hipertiroidismo cuando los pacientes con UCI responden mal a la terapia con antihistamínicos, ya que un tratamiento precoz de la enfermedad de Graves mejora significativamente la urticaria.

Palabras clave: Urticaria crónica. Enfermedad de Graves

Introduction

Organ-specific antibodies are present in about 30% of patients with chronic idiopathic urticaria (CIU). Particularly interesting is the high rate of thyroid autoimmunity characterized by the presence of antithyroid peroxidase (TPO) antibodies [1-6]. More recently an increased frequency of low levels of serum vitamin B₁₂ associated with antigastric parietal cell antibodies and chronic antral gastritis have also been described [7]. We report 2 patients with CIU who developed symptomatic hyperthyroidism within 6 months of the onset of their urticaria and who had demonstrable antithyrotropin receptor antibodies (ATRAAs).

Case 1

A 35-year-old woman presented with a 3-month history of daily urticaria that responded poorly to regular antihistamine therapy with fexofenadine 180 mg up to twice daily. Individual patches of urticaria lasted no more than 8 hours. She complained of anxiety and a sensation of heat 1 month after the onset of the urticaria. Her weight was stable and her routine blood tests (Table) confirmed anti-TPO antibodies. Subsequent thyroid function tests (TFT) showed significantly elevated levels of free thyroxine 3 and thyroxine 4 and markedly depressed levels of thyrotropin. Her urticaria was active on a daily basis and she soon developed significant

Table. Summary of Blood Tests for Both Patients. Note That Tests Were Not Necessarily Performed at the Same Time or at the Initial Presentation of Urticaria

Test	Blood Count	ESR	Free T3	Free T4	TSH	AIP	TPO	TSH-R Antibodies
Normal range		<20	3.0-6.5	10.0-23.0	0.3-5.5	Neg	<40	<0.4
Case 1	N	27	15	30	<0.01	Neg	101	23
Case 2	N	36	26.8	59.1	<0.01	Neg	40	4

Abbreviations: AIP, autoimmune profile consisting of antinuclear, antimitochondrial, anti-smooth muscle, anti-LKM and anti-gastric parietal cell antibodies. ESR, erythrocyte sedimentation rate; T, thyroxine; TPO, thyroid peroxidase; TSH, thyrotropin; TSH-R, thyrotropin receptor.

tremor with mild eyelid retraction, sweating, and weight loss (2 kg). She was started on carbimazole, and her urticaria and hyperthyroidism both improved. Her antihistamine therapy was progressively withdrawn and subsequent blood tests confirmed Graves disease with a very significant level of ATRA measured by the enzyme-linked immunosorbent assay.

Case 2

A previously healthy 41-year-old woman developed urticaria during a period of increased stress. No specific foods or drugs could be implicated and the patches lasted no more than 12 hours. The urticaria responded poorly to high-dose antihistamine therapy with cetirizine. The patient's initial blood tests (Table) were normal. However, 4 months later the patient complained of anxiety, a sensation of being hot, tremor, generalized weakness, and palpitations. Her thyroid function tests confirmed biochemical hyperthyroidism (Table). While thyrotropin receptor antibodies were detectable at this stage there was still no evidence of TPO antibodies. Treatment with carbimazole was started and the patient soon became euthyroid and a marked improvement in her urticaria was observed. When thyroid function returned to normal, urticaria was only minimally evident and was readily controlled by antihistamine therapy at conventional doses.

Discussion

The prevalence of anti-TPO antibodies in CIU has been reported to be 10% to 29% [1-6]. It appears to be more frequent in patients with CIU and a positive autologous serum skin test result than in those with a negative result [8]. Interestingly, there is also a positive correlation between anti-TPO antibodies and anti-immunoglobulin (Ig) E receptor antibodies [9].

Most studies suggest that anti-TPO antibodies are epiphenomena and not directly causative of skin wheals [10]. Kandeel et al [11] found skin biopsies to be indistinguishable by light microscopy between patients with CIU who had serological evidence of Hashimoto thyroiditis (HT) and those who did not. While only the biopsies from patients with CIU and HT together had perivascular fibrin deposits,

there was no evidence of immune complex deposition, and immunohistochemical studies showed no variation in the presence of T and B cells. Furthermore, analysis of T-cell receptor V-beta restriction in the thyroid tissue of patients with HT and the skin of patients with CIU and HT by in situ polymerase chain reaction showed no evidence of oligoclonal T-cell subpopulations.

The effects of treatment with thyroxine on the clinical symptoms of CIU in patients with anti-TPO antibodies are generally positive. However, there are no double-blind placebo-controlled studies of thyroxine treatment in CIU patients with anti-TPO antibodies and no thyroid dysfunction. For those with CIU who are biochemically and/or clinically hypothyroid, a randomized study would be difficult to justify ethically. It should also be noted that there is no uniform definition of the timescale for improvement after starting thyroxine treatment. Thus, information on the role of thyroxine replacement therapy in CIU is based on observational data, which is clearly difficult to interpret in a condition that is well known to show spontaneous resolution in most patients. Nevertheless, some studies suggest a greater improvement in CIU patients with increased thyrotropin levels [12,13], even in patients without thyroid dysfunction [14]. Others suggest that improvement, while observed, is infrequent [15]. Nonetheless, it is clear that all reports confirm the ineffectiveness of thyroxine in at least some patients with TPO antibodies with or without thyroid dysfunction. It is interesting that, at least in children, thyroid autoimmunity and overt hypothyroidism may develop several years after the onset of CIU [16].

While the frequency of anti-TPO antibodies is universally considered to be higher in CIU, there are few publications on the prevalence of ATRAs in this condition. Verneuil et al [2] found none in their 99 patients. In our own brief study of 30 patients with CIU (unpublished), we also found none. In their assessment of 154 patients with CIU, Small and Lerman [17] found 6 patients with hyperthyroidism, 4 of whom also had polycythemia vera. A causal relationship was not obvious in any of the patients based on the results of skin biopsy, complement and immune complex analysis, and assessment of IgE levels. However, Gaig et al [18] reported 2 patients with Graves disease who improved rapidly after therapeutic normalization of their thyroid function. They also found a significant improvement in CIU in 15 of their 18 patients

who had TPO antibodies with or without hypothyroidism. As with virtually all previous studies, and indeed the present one, thyroid hormone replacement and treatment of Graves disease were neither blinded nor randomized. Thus, it is difficult to be certain of the benefit of either.

Our patients were clinically euthyroid at the start of their CIU but became symptomatic within 3 months of onset of their urticaria. Their CIU also improved with normalization of thyroid function after an earlier poor responsiveness to high-dose antihistamine therapy alone. Henderson and Highet [19] observed a similar improvement in urticaria with normalization of thyroid function. They also observed a poor response to antihistamines and corticosteroids, without correction of the thyroid dysfunction. In the absence of any controlled comparison, it is difficult to be certain whether treatment of the hyperthyroidism in our patients—and in those of other authors [18,19]—was beneficial or whether there was a natural improvement of the CIU.

While Irani et al [20] noted the association between CIU and Graves disease as representing 2 conditions with antireceptor antibodies, a causal relationship with ATRA has not been established. Indeed, in patients with a positive autologous serum skin test result, it is likely to represent the well known increase in a second autoimmune disease in patients already affected by one autoimmune condition. This is also suggested by the coexistence of CIU with Graves disease in a patient with type 1 diabetes [21]. In substantiation, the improvement in CIU with normalization of thyroid function is often evident even in the continued presence of ATRAs or anti-TPO antibodies. We suggest that the rapid improvement in CIU in patients with Graves disease may be due to a reduction in the body's metabolism and the sensation of 'overheating' experienced when thyroid hyperactivity is reduced. Interestingly, many patients with CIU and no underlying autoimmunity also experience a worsening of their condition when they are hot and sweaty.

In conclusion, clinicians should exclude hyperthyroidism if CIU responds poorly to conventional treatment, as it appears to be rapidly and significantly ameliorated by normalization of raised thyroid activity.

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