Autoimmune Thyroid Disease and Refractory Chronic Urticaria: Thyroidectomy as a Treatment for Long Standing Remission. A Case Report

One Sentence Summary: A 36-year-old woman with a refractory chronic autoimmune urticaria and a concomitant autoimmune thyroid disease achieved remission from the dermatological point of view after thyroidectomy.

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Abstract
The relationship between autoimmune thyroid disease and chronic autoimmune urticaria has been well established, even though the cause is still unknown. Several medical treatments have been proposed for chronic autoimmune urticaria, being antihistamines the first line. However, not all of the cases respond to this therapy, and other alternatives have been suggested, including corticosteroids, leukotriene antagonists or immunosuppressive drugs. Clinical improvement has also been reported after performing a thyroidectomy in 9 patients.

Introduction
The relationship between autoimmune thyroid disease (AITD) and chronic autoimmune urticaria (CAU) was first described in the decade of the 1980s [1–4]. Since then, multiple cases have been reported, but its pathogenic mechanisms are not well known. CAU is a distressing disease defined as the presence of recurrent, transient and itching maculo-papular skin lesions with or without angioedema, that last more than 6 weeks [5]. Diagnosis is confirmed with an autologous serum skin test, which is considered positive if a papule bigger than 16 mm is obtained [5]. First-line treatment has been based on the use of non-sedating, second-generation antihistamines; following the recommendations of the recent international guidelines, in patients who do not respond to antihistamines at licensed doses, the daily dosage of these drugs can be increased up to 4-fold [6]. However, a significant proportion of patients with chronic urticaria remain poorly controlled; in these cases, alternative therapeutic approaches have to be considered. Nonetheless, even then, a percentage of cases remain symptomatic. We report a case of AITD and refractory CAU with complete and long-standing remission after thyroidectomy. Furthermore, we examine the medical literature for evidences supporting thyroidectomy as a treatment for refractory CAU in patients with thyroid disease.

Case Report
A 36-year-old woman was referred to a dermatology clinic due to pruritic skin lesions. She had no allergies or toxic habits. Her personal clinical history was unremarkable except for 3 episodes of paroxysmal supraventricular tachycardia, which resolved after electric ablation in 2002. The patient started having recurrent maculo-papular lesions which were compatible with urticaria in February 2009. During physical examination, a grade 1 goiter without nodules or palpable adenopathies was found. A pharmacologic, infectious or atopic aetiology was ruled out, and allergy tests were conducted, obtaining negative results. Alfa trypsin and complement factors were normal. Autoantibodies were also determined to discard connective tissue diseases. All the titres were undetectable
A cutaneous biopsy showed perivascular oedema with a lymphocytic infiltrate, compatible with urticaria (Fig. 1). A positive autologous serum skin test was obtained, and the patient was diagnosed with CAU, starting therapy with desloratadine 2 mg every 8 h.

2 months later, subclinical hyperthyroidism was detected, with TSH 0.180 mcU/ml (NR: 0.55–4.78 mcU/ml), free T4 1.06 ng/dl (NR: 0.89–1.76 ng/dl) and free T3 2.3–4.2 pg/ml (NR: 1.69–2.69 pg/ml). The titre of TSH-R antibodies was 7 U/L (NR: 0–10 U/L). A gammatography was carried out, showing a diffuse moderate hypercaptoping goiter, and ultrasonography reported an enlargement of the superior part of the right lobe (55 × 17 × 19 mm), being the left one of normal size (40 × 16 × 18 mm), without echogenicity alterations, focal lesions or adenopathies. At this point, carbimazole 5 mg per day was started.

Due to the persistence of the urticaria at that moment, 5 mg of prednisone per day were added. Euthyroidism was achieved with carbimazole and lasted 6 months. Afterwards, the patient’s thyroid function worsened with TSH 0.007 mcU/mL, free T3 15.86 pg/ml and free T4 3.84 ng/dl. Treatment with metimazole 15 mg per day was undertaken, obtaining normalization of thyroid function tests 8 weeks later. Subsequently, anti-thyroid drugs were withdrawn. However, during this period, the urticaria worsened progressively, and treatment with desloratadine 5 mg and deflazacort 6 mg during alternate days was tried out, without clinical remission.

6 months later, the patient had a normal thyroid function with persistence of positive thyroid antibodies. Due to the unresponsiveness of CAU, it was decided to perform a total thyroidectomy, and histological examination showed a diffuse hyperplasia in the context of a chronic lymphocitary thyroiditis (Fig. 2). After surgery, treatment with levothyroxine 75 mcg per day was started. Remarkably, urticaria resolved immediately after the thyroidectomy, and the patient remained euthyroid and totally asymptomatic more than 2 years later. At this point, thyroid autoantibodies were negative (last observation: January 16, 2014).

**Discussion**

A relationship between CAU and AITD has been consistently reported since 1983. In this regard, several studies have shown higher prevalence and titres of thyroid autoantibodies among patients with CAU [5, 7–12]. The greatest study published so far analysing the relationship between CAU and autoimmune disorders, compared 12778 patients with 10714 controls, and thyroid diseases were established as the most common autoimmune disorder in patients with CAU. Hypothyroidism was diagnosed in 9.8% of cases, in comparison to 0.6% of controls (p < 0.0005), and hyperthyroidism in 2.6% vs. 0.09% (p < 0.0005). MGHA were identified in 4.7% of cases, in comparison to 0.4% of the control group (p < 0.0005), and 1% had TGHA in comparison to 0.04% of controls (p < 0.0005) [12]. In the same way, O’Donell et al. suggested that the risk for positive MGHA and abnormal thyroid function is 4 and 15 times higher, respectively, among patients with a positive skin test [9]. Interestingly, 6 cases of papillary thyroid carcinoma (PTC) have also been reported in patients with CAU [13–15]. However, thyroid autoimmunity was positive only in one of them. Nevertheless, the fact that thyroidectomy achieved remission in these patients could suggest that other unknown antibodies directed towards thyroid tissue are responsible for the relationship between PTC and CAU.

The autoimmune mechanism by which urticaria is produced is mediated by the humoral immune system. In 30–40% of cases, IgG auto-antibodies against the alpha chain of the high affinity Fc receptor for IgE (FccRIα) have been described [16–18], and in 50% of them, IgG directed towards IgE [19]. These antibodies activate basophils and mast cells to release histamine, and complement fixation augments histamine release by formation of C5a anaphylatoxin [20].

On the other hand, autoimmune thyroiditis is produced due to the action of cellular immunity. In this case, there is a functional defect of suppressor cells and an activation of autoreactive T cells, which cooperate with B cells to stimulate the production of anti-thyroidal antibodies [5]. However, MGHA and TGHA-mediated complement activation has been observed in some studies, and some authors have speculated that different autoantigen-
autoantibody systems (anti-FcR\(\text{\textalpha}\), MGHA) synergize in generating C5a and triggering mast cells and basophils in patients with Hashimoto thyroiditis [21]. As well as this, the cytotoxic T-lymphocyte associated antigen 4 (CTLA4) gene has been shown to be a susceptibility factor for Hashimoto’s thyroiditis and Grave’s disease, and Brozoa et al. hypothesized that it could also have a role in CAU [22]. Furthermore, recently Ramos-Proll et al. have suggested CAU as a possible non-endocrine manifestation of autoimmune polyglandular syndrome type II [23]. However, another hypothesis is that some infectious agents could be involved in the pathogenesis of both chronic urticaria and thyroiditis. Thus, several clinical and experimental observations suggest a relationship between agents like hepatitis C virus, *Staphylococcus aureus* and *Helicobacter pylori* with both CAU and AITD [24–27].

It therefore seems logical to state that thyroid examination together with thyroid function tests and autoantibodies titration is advisable in CAU patients. It is generally accepted that CAU patients should undergo a stepwise treatment, considering that in most cases stepping-up implies an increase in both costs and adverse effects. This process considers leukotriene receptors antagonists or short courses of steroids after high doses of second generation H1 histamines. If the disease relapses or persists, needing permanent corticosteroid treatment, the next option should be cyclosporine. Even omalizumab, a monoclonal IgG antibody that binds free IgE and downregulates mast cell function, can be considered [6]. However, nowadays the evidence supporting the use of other immunosuppressive agents, anti-inflammatory drugs, anticoagulants and intravenous immunoglobulins is scarce and insufficient to recommend their routine use.

We report a case of refractory CAU associated to AITD that resolved immediately after thyroidectomy. The patient was initially hyperthyroid (depressed TSH, increased T4 and free T4 index) and increased TSH, though. 6 other cases of urticaria remission after surgery have also been described in the literature [7, 8, 9]. In the third case, autoimmunity had become negative at 6 months (Hashimoto’s) and one Graves’) [4, 30, 31]. In 2 of these cases autoimmunity had become negative at 6 months (Hashimoto’s) and 18 months follow-up (Graves’). In the third case, autoimmunity after surgery was not recorded, though. 6 other cases of urticaria remission after surgery have also been described in the context of AITD (Table 1). Unfortunately, immunological data have not been reported in all of these PTC patients. On the other hand, one case of CAU 6 years after receiving radioiodine treatment for GD has been reported. In this patient, a concurrent increase of thyroid autoantibodies was detected along with the CAU [23].

<table>
<thead>
<tr>
<th>Case Number</th>
<th>Author</th>
<th>Year</th>
<th>Age</th>
<th>Gender</th>
<th>Thyropathy</th>
<th>Autoantibodies titer</th>
<th>Follow-up</th>
<th>Time of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cailleba et al.</td>
<td>1993</td>
<td>not recorded</td>
<td>female</td>
<td>Graves’ disease</td>
<td>not recorded</td>
<td>cured</td>
<td>not recorded</td>
</tr>
<tr>
<td>2</td>
<td>Amoroso et al.</td>
<td>1996</td>
<td>60</td>
<td>female</td>
<td>thyroiditis</td>
<td>Anti-Tg 1:40 Anti-TPO &gt; 1:25 600</td>
<td>cured Anti-Tg negative Anti-TPO 1:6-400</td>
<td>18 months</td>
</tr>
<tr>
<td>3</td>
<td>Raza et al.</td>
<td>2004</td>
<td>29</td>
<td>female</td>
<td>thyroiditis</td>
<td>Anti-Tg 3 Anti-TPO &gt; 70 IU/ml and 3.0 IU/ml</td>
<td>cured</td>
<td>25 months</td>
</tr>
<tr>
<td>4</td>
<td>Manganoni et al.</td>
<td>2007</td>
<td>39</td>
<td>female</td>
<td>TPC</td>
<td>negative</td>
<td>cured</td>
<td>6 years</td>
</tr>
<tr>
<td>5</td>
<td>Manganoni et al.</td>
<td>2007</td>
<td>32</td>
<td>female</td>
<td>TPC</td>
<td>negative</td>
<td>cured</td>
<td>7 years</td>
</tr>
<tr>
<td>6</td>
<td>Manganoni et al.</td>
<td>2007</td>
<td>61</td>
<td>female</td>
<td>TPC</td>
<td>not recorded</td>
<td>cured</td>
<td>5 years</td>
</tr>
<tr>
<td>7</td>
<td>Manganoni et al.</td>
<td>2007</td>
<td>42</td>
<td>female</td>
<td>TPC</td>
<td>negative</td>
<td>cured</td>
<td>not recorded</td>
</tr>
<tr>
<td>8</td>
<td>Ozkaya et al.</td>
<td>2011</td>
<td>25</td>
<td>female</td>
<td>TPC</td>
<td>negative</td>
<td>cured</td>
<td>6 months</td>
</tr>
<tr>
<td>9</td>
<td>Kartal et al.</td>
<td>2012</td>
<td>25</td>
<td>male</td>
<td>TPC</td>
<td>Anti-Tg 300 IU/ml Anti-TPO 55 IU/ml</td>
<td>cured</td>
<td>9 months</td>
</tr>
</tbody>
</table>

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In conclusion, we describe a case of CAU associated toAITD that resolved immediately after thyroidectomy with a long lasting remission. Other cases of CAU remission after thyroidectomy have been reported in the literature. These cases together with epidemiological, clinical and experimental data suggest that these 2 entities are closely related and that thyroidectomy could benefit the course of CAU by removing thyroid antigens. Furthermore, thyroidectomy should be considered in patients with CAU andAITD when third and fourth-line treatment options are being needed for the treatment of the skin lesions (Fig. 3).

Conflict of interest: The authors declare no conflict of interest.

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Fig. 3. Therapeutic algorithm for CAU in patients with AIITD.