Chronic urticaria associated with occult papillary thyroid carcinoma and dramatic improvement after total thyroidectomy: A retrospective study from Turkey

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**Key words:** Thyroid carcinoma; papillary; chronic urticaria; thyroid ultrasonography; thyroidectomy.

**Palabras clave:** Carcinoma de tiroides. Papilar. Urticaria crónica. Ultrasonografía de tiroides. Tiroidectomía.

Chronic urticaria (CU) is characterized by recurrent hives lasting more than 6 weeks, alone or in combination with angioedema, and may persist for months to years [1]. It is further classified as spontaneous or inducible urticaria such as dermographic, cholinergic, aquagenic, solar, or cold-, heat-, or pressure-induced types. Several triggers were proposed, such as foods, drugs, infections, autoimmune comorbidities including autoimmune thyroid disease, and malignancies [1]. Recent reports indicated associations with hematological malignancies such as leukemia, lymphoma, and myeloma, as well as with carcinoma of the lung, bladder, testis, ovary, and thyroid gland, in particular papillary thyroid carcinoma. The dramatic recovery from urticaria after total thyroidectomy in the reported cases with thyroid carcinoma suggests a causal relationship (Table 1) [2-5]. The aim of this study was to analyze the frequency and treatment outcomes of thyroid carcinoma among patients with chronic urticaria.

A total of 359 patients who were diagnosed with CU including both spontaneous and inducible types based on their clinical findings and provocation test results at our dermatoallergy clinic between 2010 and 2018, underwent a routine thyroid work-up. This included thyroid stimulating hormone (TSH) level, thyroid function tests (free thyroxine, free triiodothyronine), thyroid antibodies (anti-thyroglobulin [TG] and anti-thyroperoxidase [TPO]), and a thyroid ultrasonography, the latter as the “key diagnostic tool” to suspect
thyroid carcinoma in otherwise asymptomatic patients. Fine-needle aspiration biopsy was performed if there was any suspected nodule of ≥ 10 mm in diameter in the thyroid ultrasonography. Those with malignant or suspicious cytology underwent total thyroidectomy. Patients diagnosed with thyroid carcinoma in the histopathology, were evaluated in regard to the duration of the disease, age, gender, and treatment outcomes using the weekly urticaria activity score (UAS7). Focal or systemic infections, food or drug allergy, and urticarial vasculitis were ruled out. 118 patients showed elevated levels of thyroid autoantibodies, and 21 had abnormal results in their thyroid function tests or TSH level. A total of 30 patients had previously known thyroid disease (14 of them had elevated levels of thyroid autoantibodies, and 7 had abnormalities in their thyroid function and/or TSH tests), such as Hashimoto’s disease (n=23), benign multinodular goiter (n=3), operated papillary thyroid carcinoma (n=2), hypothyroidism of unidentified etiology (n=1), and hyperthyroidism (n=1). The thyroidectomy operations of the 2 patients with papillary thyroid carcinoma took place 8-9 years earlier than the onset of urticaria.

Suspected nodules of ≥ 10 mm in diameter were identified in the thyroid ultrasonography of 27 patients, who subsequently underwent fine needle aspiration biopsies. Cytology was malignant in 5 patients, suspicious in 2 patients, and benign in the remaining. All 5 patients with malignant cytology underwent total thyroidectomy. Histopathology showed occult papillary thyroid carcinoma in 4 patients, and occult papillary/follicular thyroid carcinoma in 1 patient (Table 1). Patients were exclusively female. The mean age of onset of urticaria was 29.8 years (range: 7-59 years). None of them had a prior history of thyroid disease or other autoimmune disorder. There were no clinically palpable thyroid nodules. Thyroid function tests, serum levels of TSH and thyroid autoantibodies were within normal limits. Four of the patients had chronic spontaneous urticaria and one patient chronic inducible urticaria, ie,
aquagenic urticaria. The latter was described in detail in a recent report [2]. No other triggers for urticaria could be found, and patients were on regular antihistamine therapy. The median lag time between the onset of urticaria and diagnosis of thyroid carcinoma was 6 months (range: 4 months-4 years). The prevalence of thyroid carcinoma-associated chronic urticaria was 1.4% (n=5).

Total remission of urticaria was achieved in 4 patients within 1-2 days following total thyroidectomy. The UAS7 decreased from a mean score of 32.2 (range: 21-42) to zero in all patients. Urticaria did not recur in these patients in a median follow-up period of 47 months. One patient showed an 80% remission rate of her urticaria the day after the operation. Urticaria resolved completely within 2 weeks and did not recur during a 2-year follow-up. Two patients with suspicious cytology underwent total thyroidectomy as well. Both had benign histopathology. One of these patients with intermittent chronic urticaria reported that she was free of attacks after surgery and in a 5-year follow-up while on therapy with thyroid hormones. The other patient was lost to follow-up after the surgical procedure.

The incidence of thyroid carcinoma is increasing worldwide, probably also due to easier detection of occult cases. Papillary thyroid carcinoma is the most frequent type of thyroid carcinoma and has a female preponderance [6]. It also seems to be the main type of thyroid carcinoma associated with urticaria. Recent reports showed a significant association of papillary thyroid carcinoma with chronic spontaneous urticaria in 4 patients [3], and acute urticaria in 1 patient [4], almost exclusively females (Table 1). Follicular thyroid carcinoma was associated with isolated angioedema in 1 patient [5]. In two other cases, angioedema-like lesions were seen as a result of superior vena cava obstruction secondary to thyroid carcinoma [7,8]. The dramatic improvement of urticaria in a very short period following total thyroidectomy in the present study as well as in previously published reports (Table 1) was striking. This suggests a causal relationship between urticaria and thyroid carcinoma, rather
than a coincidence. All patients had occult thyroid carcinoma that could only be suspected by thyroid ultrasonography. Similar to our study, thyroid autoantibodies, TSH, and thyroid function tests were within normal limits in all of these previously reported patients except in one case with elevated levels of TPO antibodies [9]. Urticaria persisted only in this case [9]. Her TPO antibodies normalized after thyroidectomy and the authors suggested that her urticaria could have been complicated by insufficiently suppressed TSH postoperatively [9]. Interestingly, one of our patients who underwent a total thyroidectomy due to a suspicious cytology that finally resulted benign, reported that she had no more attacks of urticaria after surgery and in a 5-year follow-up.

The real prevalence of thyroid carcinoma in patients with CU remains to be determined. A population-based cohort study from Taiwan reported an increased risk of thyroid cancer in CU without giving further details [10].

Our study shows that a routine thyroid ultrasonography alone might serve as a life-saving diagnostic tool in CU patients who were “asymptomatic” for thyroid carcinoma, and prevent these patients from expensive and unnecessary long therapies of CU. As the most striking finding, CU resolved dramatically in all of the 5 patients with thyroid carcinoma within 1-2 days following total thyroidectomy. Therefore, we would suggest ultrasonographic screening of the thyroid gland in every patient with CU, regardless of the results of TSH / thyroid function tests or serum levels of thyroid antibodies.
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References


Table Legends

Table 1. Characteristic features of the patients in the present study and in previous reports (TSH, thyroid stimulating hormone; TFT, thyroid function tests; CSU, chronic spontaneous urticaria; TR, total remission; NM, not mentioned; TPO, thyroperoxidase).
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<table>
<thead>
<tr>
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<th>Diagnosis</th>
<th>Thyroid autoantibodies</th>
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<th>Thyroid carcinoma</th>
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<th>Follow-up</th>
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<td>25-55</td>
<td>4 months-4 years</td>
<td>4 CSU, 1 aquagenic urticaria</td>
<td>Normal</td>
<td>Normal</td>
<td>4 papillary, 1 papillary/ follicular</td>
<td>TR in 1 to 2 days</td>
<td>7 months-2 years</td>
</tr>
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<td>Manganoni [3]</td>
<td>4 Female</td>
<td>32-61</td>
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<td>4 CSU</td>
<td>Normal</td>
<td>Normal</td>
<td>4 Papillary</td>
<td>TR in 1 to 4 days</td>
<td>5-7 years</td>
</tr>
<tr>
<td>Kartal [4]</td>
<td>1 Female</td>
<td>25</td>
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<td>Normal</td>
<td>Normal</td>
<td>Papillary</td>
<td>TR in 2 days</td>
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<td>Vallent [5]</td>
<td>1 Male</td>
<td>43</td>
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<td>Angioedema</td>
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<td>Ravindran [9]</td>
<td>1 Female</td>
<td>51</td>
<td>3 months</td>
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