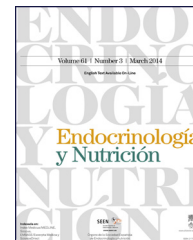




ENDOCRINOLOGÍA Y NUTRICIÓN

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EDITORIAL

Chronic autoimmune thyroiditis and thyroid cancer[☆]



Tiroiditis crónica autoinmunitaria y cáncer de tiroides

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The relationship between chronic autoimmune thyroiditis and mucosa-associated lymphoid tissue (MALT) thyroid lymphoma is well known.¹ By contrast, its relationship to thyroid follicular epithelium cancer, such as papillary carcinoma, has been for a long time and continues to be controversial, because the concept of chronic inflammation leading to neoplasia is also well established in other tissues. Coexistence of chronic thyroiditis and differentiated thyroid carcinoma is a real clinical situation whose significance is still unknown²; in addition, thyroiditis itself may sometimes be associated to both papillary thyroid carcinoma and MALT lymphoma.³

The first difficulty lies in that the criteria for defining autoimmune thyroiditis are quite heterogeneous, as are the patient groups studied, which may be surgical series or cytological studies with no subsequent surgery. Differentiation between chronic thyroiditis as a nosological entity and lymphocyte infiltration may be another confounding factor. In this regard, such infiltration represents that the immune system, through lymphocytes, could locate the tumor, and thus prevent recurrence. This potential mechanism has led to consider immunotherapy in advanced thyroid cancer, as there would be a generalized immune defect, and a response to cancer could be triggered by tumor cells or specific tumor antigens. An alternative explanation to lymphocyte infiltration is that the tumor itself acts locally, triggering a

reaction against the host, which would not be generalized, although low titers of thyroid gland antibodies have been found in reported series.^{4,5} An additional possibility is that lymphatic blockade by tumor thrombi interferes with normal lymphatic return, which would explain the presence of lymphocyte infiltration in the diffuse sclerosing or tall cell variants with nodal invasion or in the exceptional cases of follicular carcinoma where it also occurs.^{4,5}

The Warthin variant, a subtype of oncocytic papillary carcinoma, has also been seen to be associated to Hashimoto thyroiditis and to have a good prognosis.⁶

Relationships between both conditions are therefore diverse and imprecise, and the factors determining such an association are unknown. Patients with Hashimoto thyroiditis do not appear to have a greater prevalence of cancer in thyroid nodules as compared to those without this disease.^{7,8} On the other hand, positive anti-thyroglobulin antibodies, but not positive anti-thyroid peroxidase antibodies, have been seen to be independent predictors of thyroid nodule malignancy, regardless of the presence or absence of chronic thyroiditis; in addition, a positive antibody test is related to higher thyroid-stimulating hormone (TSH) levels. That is, presence of such antibodies, combined with TSH levels, may provide additional information, together with other clinical data, for predicting risk of malignancy in nodules with indeterminate cytology.^{8,9} Moreover, an additional study showed that preoperative TSH levels are directly related to more advanced tumor stages and to the presence of nodal neck metastases; by contrast, presence of anti-thyroglobulin antibodies does not appear to be a prognostic marker.¹⁰

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Association between lymphocytic thyroiditis and papillary thyroid carcinoma appears to be established,¹¹ especially in areas with a high prevalence of chronic thyroiditis, such as some Chinese regions; the basis of such relationship would be long-term TSH elevation, which is considered an ideal risk factor for development of thyroid carcinoma.¹² Concomitant occurrence of both would be particularly evident in iodine-rich areas, because iodination increases thyroid autoimmunity. Papillary carcinoma has been found to be more common in nodules in the setting of Hashimoto thyroiditis and with higher TSH levels; prevalence would decrease in subjects treated with L-thyroxine.¹³ It is estimated that the change of papillary thyroid carcinoma would increase by 11% per each mIU/L increase in TSH, and that tumor size would be greater. On the other hand, risk of papillary carcinoma is lower in patients with autonomous toxic nodules, in whom TSH levels are lower.^{14–16}

A systematic analysis of medical literature on the association between lymphocytic thyroiditis and thyroid carcinoma suggests that no evidence exists of a correlation in series based on thyroid cytology samples, while studies of thyroidectomy specimens have reported such evidence. Prevalence of papillary carcinoma in patients assessed by cytology is 1.2%, but increases to 27.5% in studies performed on thyroidectomy specimens. The difference may be due to bias induced by patient selection for surgery. The controversy cannot be considered to be resolved.^{17,18} The relationship initially seen between thyroid cancer and Graves-Basedow would not be defined either.¹⁹

Different studies have shown that concurrent chronic lymphocytic thyroiditis and papillary carcinoma are associated to better tumor prognosis, including a lower frequency of nodal metastases, as has been seen in women with stage pT1a papillary carcinoma,^{20–26} and has also been reported for nodal involvement of the central compartment.²⁷

From the immune viewpoint, cytotoxic CD3–CD16 and CD56dim cells account for 95% of the NK population, and immunoregulatory CD3–CD16–CD56 bright cells for the remaining 5%. Proliferation of T and B lymphocytes and thyroid tissue destruction result from a decrease in CD16–NK cells. They have been shown to be increased when both conditions, cancer and chronic thyroiditis, coexist and to be decreased in the presence of cancer alone, in which case they would not be able to suppress tumor progression, hence the correlation with more advanced tumor stages.²⁸

Elevated TSH levels may also predispose to the *BRAF* mutation, as seen in mouse models. This mutation is related to extrathyroid extension, lymphatic invasion, and more advanced tumor stages.²⁹ In the Korean population, however, the *BRAF*^{V600E} mutation is not associated to greater prevalence of Hashimoto thyroiditis in papillary cancer.³⁰ Another study showed that expression of RET, RAS, and ERK proteins is greatly increased in papillary carcinoma cells and oxyphil cells of Hashimoto thyroiditis, although the functional significance of the RET/PTC-RAS-BRAF cascade in both conditions has not been elucidated yet.³¹ Activation of the TSH receptor may also be significant in stimulation of the Akt pathway, which is important for tumor progression and metastasis; it is not clear, however, to what extent it may influence triggering of a more aggressive disease.³¹

The relationship between both conditions is therefore unclear. It should be elucidated whether chronic thyroiditis predisposes to development of papillary carcinoma, carcinoma is a concurrent incidental finding, or thyroiditis is part of a host response to the tumor.¹⁷ Concomitant occurrence of both conditions represents a challenge for clinicians, who see this association with some frequency and face a number of issues pending clarification with the help of information from basic research. For the time being, and in the absence of stronger evidence, patients with Hashimoto thyroiditis, and mainly those with the nodular variant, must be regularly monitored, and the possibility of development of papillary carcinoma (which is uncommon) must be considered either at diagnosis or during follow-up.

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