Editorial: The Association between Lymphocytic Thyroiditis and Papillary Thyroid Cancer

In the current issue our colleagues from Casablanca reconfirm a long-known, yet underrecognized, association between Hashimoto's thyroiditis (HT) and papillary thyroid cancer (PTC). They also confirm the female preponderance of PTC patients whether or not they have HT. They make 2 new important observations in their cross-sectional study of 348 patients with histologically confirmed PTC:

- At surgery, tumor size was significantly smaller in the HT group than the non-HT group.
- At diagnosis TNM tumor stage was significantly lower in the HT group than in the non-HT group.

It seems worthwhile to explore possible reasons for the observed associations as well as for the apparently more favorable tumor size and stage at diagnosis observed in patients with HT.

Autoimmune disorders generally, including HT, are more common in females than in males in most mammalian species and many theories have been advanced as to why this is so. One of the more interesting is that the exposure of the mother to the chimeric antigens of her offspring during labor and delivery sets off an immune response to those antigens. Through molecular mimicry, that immune response later may interact with the mother's own antigens. This interesting hypothesis does not explain, however, why females who have never been pregnant are still more subject to autoimmune disorders than males.

Some authors have considered the association between HT and PTC to be merely fortuitous [1, 2].

The present authors note that the association may be due to shared mutations in the oncogenes RET and PTC in both disorders or to shared alterations in protein p63 expression as reported by a number of groups [3-8].

They also cite a study that suggests that autoimmune reaction may actually be caused by a pre-existing PTC [9].

Many groups have suggested that chronic, low grade inflammation, which characterizes many autoimmune disorders, like HT and Graves' disease (GD) predisposes to cancer [10].

A number of authors [11-14] cited in the present article suggest that the elevated serum TSH levels encountered in a high percentage of patients with HT contribute to the risk for developing PTC, since TSH not only stimulates thyroid hormone synthesis by thyroid follicular cells, but also stimulates follicular cell growth and division. Thyroid stimulating immunoglobulin, which acts through binding to the TSH receptor may fulfill a similar role in patients with GD who are also predisposed to PTC.

Still another consideration is that patients with HT, like patients with GD are reported to be insulin resistant [15-17]. We have also reported that autoimmune disorders, including HT and GD are almost universally associated with non-classic adrenal hyperplasia, a group of disorders in which insulin resistance plays a pivotal role in the biochemical and clinical expression of the enzymatic defects [18]. HT has also been associated with polycystic ovarian syndrome (PCOS) [19], a disorder defined by insulin resistance. Insulin resistance generally only directly affects carbohydrate/lipid metabolism and spares growth promoting and pro-inflammatory effects of insulin

mediated through the MAP-kinase pathway. A role for insulin resistance is now widely recognized in the pathogenesis of several common cancers, including breast, colon, and prostate, and insulin resistance is reported to be a feature of PTC as well [15].

Vitamin D deficiency contributes to insulin resistance and is part of the pathogenesis of many autoimmune disorders and is also believed to contribute to the pathogenesis of several cancers which are associated with insulin resistance. The fact that in many societies women tend to stay indoors more than men and cover their skin more than men when they do venture outside may contribute to more widespread and more severe Vitamin D deficiency in women and ultimately to more autoimmune disease and PTC.

Finally, we need to consider the possible role of surveillance in explaining the higher prevalence of PTC in HT patients. Worldwide, there has been an impressive increase in the number of cases of differentiated thyroid cancer being diagnosed. While some of this increase is doubtless an actual increase in the incidence of these cancers, some of this increase is due to improved surveillance for thyroid cancer, especially with widespread use of high resolution ultrasound and ultrasound-guided fine needle aspiration of non-palpable thyroid nodules. Patients who are already known to have HT are more likely than those who do not to undergo more scrutiny of their thyroids and thus have thyroid cancer diagnosed more frequently, at a smaller size, and a lower TNM stage.

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