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Editorial

Is Grave´S Disease A Risk Factor for Papillary Thyroid Carcinoma? Should We Be Actively Screening?

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Hyperthyroidism is a rather common disease, with prevalence rates, In the United States, of approximately 1.2% of the population [1]; diffuse toxic goiter, otherwise denominated Grave´s disease (GD), is the most common cause of hyperthyroidism globally [2], but its association with thyroid papillary carcinoma remains uncertain.

While the incidence of thyroid malignancies rises in the whole world, reaching escalating numbers of 7% to 15% of the patients harboring a nodule, depending on age, sex, family history, and other factors [3,4], the malignancy rate of palpable thyroid nodules in GD patients ranges from 2% to up to 55% [5,6].

Current case series and cohorts rise even more questions regarding the aggressiveness of thyroid cancers in GD patients. Aggressive behavior has been identified by some reports, including increased rates of para-thyroidal invasion and lymphatic metastasis [6-8]. Mortality rates seems to also be higher in GD patients, and that remains a fact independently of tumor size [9-11], though this has not been confirmed by other case series [12,13].

A recent systematic review and metanalysis [14] showed a 45% higher risk of multifocality/multicentricity, and over 2 times a higher risk of distant metastasis, but no statistically significant increase in malignancy-related mortality and recurrence.

In the past, thyroid cancer and thyroid autoimmune diseases seemed to be opposite conditions, but with this aforementioned revelation, scientists begun to study the interplay between thyroid autoimmunity and cancer. In fact, it is now clear that, in cancer development, continuous genetic abnormalities accumulation is vital to malignant behavior. The immune system could, then, be allowing or even promoting of the progression for a tumor [15].

In the histopathology of thyroid tumors, it is rather common to find various immune "reactive" cells, called Tumor-associated leukocytes and macrophages surrounding it. These cells play an expressive role in the progression of the cancer, where Macrophage phenotype M2/repair stimulate tumor growth, and macrophages M1/kill-type inhibit tumor growth [16]. In GD associated cancer, the macrophages profile is of a mixed nature, with predominance of M1 phenotype [17], which would confer protection against malignancy, but this is still a matter for further research, for there is scant data.

Another critical role in the association between autoimmune thyroid diseases and cancer is stimulation of TSH-receptor – the most potent stimulant of follicular thyroid cells growth. The association of higher levels of TSH and elevated risk of thyroid cancer has been depicted in various studies [18,19], but the same cannot be firmly stated about Thyroid Receptor Antibody (TRAb) – no concise relation has been found between TRAb and the incidence of thyroid cancer or its aggressiveness [20,21].

Keeping all these findings in mind, the exact physiopathology playing the association of Grave´s disease and papillary thyroid cancer remains uncertain, but this should not prevent clinicians from recognition of robust epidemiological data. As far as we can interpret it, early diagnosis and an aggressive approach should be considered for patients presenting Graves disease, as it has been suggested by Pellegrini [8].

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