

Hashimoto's Thyroiditis and Cancer

REVIEW

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Abstract

Background: No consensus exists on the association between Hashimoto's thyroiditis (HT) and cancer. To resolve this controversy, this review aimed to evaluate the relationship between the two conditions.

Methods: Using pub-med database, we searched studies relevant to the topic focusing on the association between HT and papillary thyroid cancer (PTC), as well as the association between HT and primary thyroid lymphoma (PTL).

Findings: Both HT and PTC are common worldwide, and the two conditions may be closely related. However, the relationship remains controversial. Some studies found that PTC coexisted with HT 2.8-fold more frequently, with variable prevalence ranging from 0.5 to 30%. In contrast to surgical and pathological series that suggested a positive correlation between the two diseases and even a cause-and-effect relationship, the other studies evaluating fine-needle aspirate specimens did not find a statistically significant correlation. On the other hand, the relationship between PTL and HT appears well established.

Conclusion: The existing data provide inconsistent evidence favoring a causal relationship between HT and PTC. Prospective studies are needed to further elucidate the relationship. However patients with HT are at risk for PTL. Therefore careful observation and follow-up of HT patients is recommended.

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Introduction

Hashimoto's thyroiditis (HT) –chronic lymphocytic thyroiditis or autoimmune thyroiditis– is the most common autoimmune thyroid disease and the most common non-iatrogenic cause of hypothyroidism [1]. This condition was first described in 1912 by Hakaru Hashimoto,

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a Japanese surgeon and pathologist [2]. Its unclear pathogenesis strongly indicates an autoimmune back-ground characterized by gradual autoimmune mediated thyroid failure with occasional presentation as a goiter. The pathology consists of diffuse lymphocytic infiltration, fibrosis, and parenchymal atrophy. It occurs in 0.3-1.5 per 1,000 individuals worldwide, is more predominant in females with a female/male prevalence ratios of 5 to 20/1 [3] and is most prevalent between 45 and 65 years of age [4].

HT is sometimes encountered in thyroids resected for a neoplastic process. The most frequent association is noted between papillary carcinoma of the thyroid (PTC) and HT. Studies have shown that HT may indeed be a risk factor for developing this type of cancer. On the other hand, the relationship between thyroid lymphoma (PTL) and HT appears well established.

Hashimoto's thyroiditis and papillary thyroid cancer

Similar to Hashimoto's thyroiditis, PTC is a relatively common disease. It is the most prevalent type of thyroid cancer, representing 70-80% of all diagnosed thyroid cancers [5, 6]. It is the 7th most common cancer among women in the world [7], and occurs more frequently in women with a female/male prevalence ratios ranging from 2.5 to 4/1 [8].

Both HT and PTC are common worldwide, and the two conditions may be closely related. This relationship was first proposed by Dailey, *et al.* in 1955 [9]. Since this initial description, the association between the two diseases has been highly debated in the literature and the relationship remains controversial. Some studies found that PTC coexisted with HT 2.8-fold more frequently, with variable prevalence ranging from 0.5 to 30% [9]. This coexistence may merely represent a chance occurrence of 2 relatively common diseases or may be indicative of a cause and effect relationship, or at least a predisposing factor. In contrast to surgical and pathological se-

ries that suggested a positive correlation between the two diseases and even a cause-and-effect relationship, the other studies evaluating fine-needle aspirate specimens did not find a statistically significant correlation between autoimmune thyroiditis and thyroid cancer [10].

In a retrospective study including 1,198 patients who underwent thyroidectomy, 18% (217 patients) were diagnosed with HT based on final pathology, and those had a higher rate of PTC overall compared to those without HT (29% vs. 23%, $p=0.051$). Female patients with HT showed a more dramatic difference in the incidence of PTC contrasted to females without HT (29% vs. 22%, $p=0.033$). On the other hand the data from male patients did not yield statistically significant results most probably due to the small sample size. The authors concluded that there was a trend in HT patients for the coexistence of PTC; a finding that becomes statistically significant in female HT patients that have 30% increased risk of having PTC compared to women without HT [11].

In another large retrospective study including 6,109 patients treated with thyroidectomy, there were 653 patients with a final diagnosis of HT. More PTC was found in those with HT than those without HT (58.3 % vs 44.3%; $p<0.05$), emphasizing the close relationship between these 2 disorders [12].

However in another retrospective cohort in which fine needle aspirate results of 10,508 patients were analyzed, there was no statistically significant association between the presence of PTC and HT. The prevalence of PTC was 1.9 % in patients with HT versus 2.7% in those without HT (RR=0.717; 95% CI 0.51-1.003) [13].

There have been a number of proposed hypotheses to explain the linkage between the two diseases. It has been proposed that the activated inflammatory response present in HT creates a favorable setting for malignant transformation. The inflammatory response may cause DNA damage through formation of reactive oxygen species, re-

sulting in mutations that eventually lead to the development of PTC.

From a histological perspective, Tamimi et al assessed the prevalence and severity of thyroiditis among three types of surgically resected thyroid tumors and found a significantly higher rate of lymphocytic infiltrate in patients with PTC [14]. Again PTC with concurrent HT is associated with female gender, young age, less aggressive disease such as small tumor size, less frequent capsular invasion and nodal metastasis, and better prognosis [15, 16]. Furthermore, these patients are also less likely to develop recurrence and have a higher survival rate [14, 15, 17, 18], mostly explained by the fact that the autoimmune response to thyroid specific antigens in patients with HT may be involved in the destruction of cancer cells expressing thyroid specific antigen in PTC. However, it remains unclear whether or not the presence of HT affects the biologic behavior of PTC, although the association between HT and PTC has been reported in many studies [9, 15, 18, 23]. It has also been reported that interleukin-1 secreted by infiltrating lymphocytes inhibits human thyroid carcinoma cell growth [24]. Therefore, destruction of tumor cells via humoral and cytotoxic T cell-mediated immune mechanisms might be related to the favorable effect of HT on PTC.

At the molecular level, activation of the mitogen activated protein kinase (MAPK) signaling pathway may represent the key molecular event linking autoimmune thyroiditis and thyroid cancer [25]. Larson and colleagues found increased phosphorylated protein kinase B (AKT) expression in regions of HT and thyroid cancer [26]. Moreover, p63 protein is commonly expressed in both diseases. Pluripotent p63-positive embryonal stem cell remnants may undergo oncogenic change leading to PTC, or may trigger an immune reaction resulting in HT [27]. Furthermore, RET (Rearranged during transfection) proto-oncogene/PTC rearrangement was more often present in PTC associated with autoimmunity,

whereas BRAFV600E mutation was more frequent in cancer without thyroiditis. It is therefore possible that chronic inflammation causes an unstable chromatin conformation and triggers RET/PTC rearrangements in thyroid epithelial cells. It is well established that the RET/PTC oncogene stimulates downstream RAF kinase and activates the MAPK cascade [28].

Another hypothesis for the causal relationship between HT and PTC is that elevated levels of TSH found in hypothyroid patients with HT stimulate follicular epithelial proliferation, thereby promoting the development of papillary carcinoma [20, 29-31].

Although many theories were proposed to explain the association between these two diseases, however, it remains unclear whether: (1) HT predisposes patients to develop PTC, (2) HT is an incidental finding with concurrent PTC, or (3) HT is a part of the host tumor response system.

To date, there are no unambiguous indications for determining whether an autoimmune disease predisposes the patient to develop cancer or whether in the course of carcinogenesis-associated cellular transformations, there occurs a change in autoimmune responses that would facilitate the development of such a disease.

Hashimoto's thyroiditis and thyroid lymphoma

Thyroid lymphoma is another malignant neoplasm that has been described in patients with HT. Although the etiology of malignant lymphomas in general, except for some types of virus associated lymphoid malignancies [32-35], is still obscure, however, autoimmune diseases have been suggested to be an etiologic factor from the viewpoint of immune disturbances [36]. Associations between antecedent autoimmune diseases (such as Sjogren's syndromes [37] and rheumatoid arthritis [38]) and malignant lymphomas have been reported, as well as the association between thyroid lymphoma and HT [39-44].

Primary thyroid lymphoma (PTL) is a rare cause of malignancy, accounting for <5% of thyroid malignancies [45] and < 2% of extra-nodal lymphomas [46, 47], with an annual estimated incidence of 2 per 1 million [48]. Women are more commonly affected than men (2-8:1) [47, 49, 50]. Patients typically present in the sixth or seventh decade of life, with men often presenting at a younger age than women [49-52]. Most thyroid lymphomas are non-Hodgkin's lymphomas (NHLs) of B-cell origin.

Patients with HT are at greater risk for developing PTL. Observational studies in Japan have estimated the relative risk of developing thyroid lymphoma in patients with HT to be 67 to 80 times higher than those without thyroiditis [44, 53]. It is widely accepted that a causal relationship exists [54]. The transformation from thyroiditis to PTL occurs in about 0.5% of cases [44, 55]. Although most thyroiditis cases do not proceed to lymphoma, most cases of lymphoma do arise in a background of thyroiditis, which is estimated to occur in approximately 60-90% of PTL cases [48, 55, 56]. The time interval between the diagnosis of HT and the subsequent development of thyroid lymphoma is in the order of 9-10 years [53].

Markedly increased incidence of primary thyroid lymphomas in patients with HT strongly suggests a pathogenetic link between these two disorders [48, 56-59]. In addition to the clinical or statistical relation between the two diseases, the pathological features of HT, which shows notable lymphocytic infiltrates in sheets and follicles with germinal centers, suggests the possibility of the progression to monoclonal growth of lymphoid cells. Various theories have been proposed to explain the basis for the evolution from thyroiditis to PTL, with one hypothesis being that chronic inflammatory stimulation of lymphocyte proliferation in HT, may be one of the major risk factors for the development of malignant lymphoma [60]. In the thyroid gland, autoantibodies against thyroid follicular epithelia might play an important role in developing in-

flammation associated lymphoma. To note that most inflammation associated lymphomas are of the B-cell subtype, with few case reports available in the literature of T-cell lymphomas associated with HT [59, 61-69]. HT is an autoimmune disease associated with a dysfunction in thyroid-specific suppressor T cells (CD8+). This lack of suppressor T-cell function could lead to an increased helper T-cell population (CD4+), and that could stimulate antithyroid B cells to proliferate.

However, the relation between Hashimoto's disease and thyroid lymphomas remains obscure. Whether the presence of lymphocytes in the thyroid provides the tissue in which the lymphoma can develop or chronic stimulation of the lymphocytes predisposes the cells to develop malignant clones has not been defined.

This association between PTL and HT has been reported in many studies since the late 1950s, most of which have been based on coexisting lymphoma and thyroiditis [39-43]. Later on in 1985, follow-up studies carried out by Holm *et al* in Sweden [44] and by Aozasa *et al* in Japan [70] confirmed the etiologically important role of HT in the development of thyroid lymphoma. Aozasa *et al*, in their large retrospective cohort study that included 5,592 female patients with chronic thyroiditis, found that 8 new cases of primary thyroid lymphoma were observed in the Hashimoto group (O) from a total of 45,623 person-years vs no cases in the Grave's group (control group), all of which were of B-cell type. The expected number of cases with thyroid lymphoma was 0.1 (E2), and the ratio O/E2 was 80 ($p < 0.001$), whereas in the control group, an increased risk of thyroid lymphoma was not observed. These findings suggested that the autoimmune reaction present in HT may play an important role in the etiology of thyroid lymphomas [70].

Most, if not all, cases of thyroid lymphoma arise in a setting of HT, and it is the distinction between HT and low-grade lymphoma that causes the most

difficulty. Traditionally, open surgical biopsy was felt to be necessary to differentiate thyroid lymphoma from thyroiditis and anaplastic carcinoma. However, with recent advances in immunophenotypic analysis and the addition of further studies such as immunoglobulin light chain restrictions, gene rearrangements, and DNA flow cytometry on FNA material of a clinically suspicious lymphoma, the accuracy of FNA has improved with a reported rate of 80-100% [71-73]. However, in any setting in which there is doubt about the FNA result, open biopsy should be done.

Hashimoto's thyroiditis and other cancers

Besides its association with thyroid cancer and thyroid lymphoma, a number of studies have examined the possible association of HT with other types of cancer. Patients with HT had an increased risk of myeloproliferative and lymphoproliferative neoplasms [44]. A doubled risk of lung cancer with HT was also reported [74]. In addition, patients with HT were at higher risk for breast cancer than those in the control group [75, 76]. The possible interactions between these two organs are eventually based on the common property of the mammary and thyroid epithelial cell to concentrate iodine, as well as on the presence of TSH receptors in fatty tissue, abundantly present in the mammary gland [77]. Moreover, recent data suggest a better breast cancer prognosis in cases with thyroid antibody positivity [78]. However, a number of studies did not observe such a positive association with breast cancer [44, 79], and lung cancer [44].

Furthermore, Chen *et al.* in a nationwide cohort study found that patients with HT had a statistically significant higher incidence density ratio of colorectal, breast, uterus, prostate, kidney, thyroid and haematologic cancer compared with the comparison cohort suggesting that thyroiditis might be a precancerous condition [80]. A possible explanation for the association of autoimmune thyroiditis with several types of cancer could be the chronic

inflammation [81, 82]. However, the pathogenetic mechanism of the interaction between HT and cancer remains unclear.

Conclusion

A century after the original description of the disease, HT continues to be a subject of considerable interest due to its association with several types of cancer, most notably thyroid lymphoma and PTC. Although the existing data provide inconsistent evidence favoring a causal relationship between HT and PTC and prospective studies involving a large number of subjects and long-term follow-up are needed to further elucidate the relationship, however, patients with HT are at risk for development of thyroid lymphoma and possibly thyroid carcinoma. Therefore,

careful observation and follow-up of HT patients is recommended, especially those with nodular variants.

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