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REVIEW ARTICLE

Papillary Thyroid Cancer and Hashimoto's Thyroiditis: An Association Less Understood

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Abstract Hashimoto's thyroiditis (HT), part of the spectrum of autoimmune thyroid diseases is a major cause of thyroid hypofunction worldwide. Papillary thyroid carcinoma (PTC), the most prevalent of all thyroid carcinomas has been associated with HT. Literature on this association are based on preoperative FNA or post thyroidectomy histopathology reports, which are subject to potential biases. Molecular, hormonal and histopathalogical basis of this association has been hypothesized, however a definite causal association has not been proved till date. This review aims to study the basis of this association and clinical features and management of HT concurrent with PTC. There are no distinctive clinical or radiological features that categorically differentiates HT concurrent with PTC from PTC or which can pick up a nodule harboring PTC in setting of HT. Smaller nodule size and radiological features like hypoechogenecity; hyper vascularity and calcification in a clinical setting of hypothyroidism have a higher odds ratio for malignancy and merit further investigations. PTC associated with HT has been seen to be less aggressive with earlier presentation with lesser chances of extra thyroidal extension and lymph nodal metastasis. The management and follow up of PTC in HT is no different from that of PTC alone. The prognosis of PTC concurrent with HT is better compared to age and stage matched PTC in terms of lower recurrence and disease free and overall survival.

Keywords Hashimoto · Thyroidits · Papillary thyroid cancer

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Introduction

Hashimoto's thyroiditis (HT), also known as chronic lymphocytic or autoimmune thyroiditis, is a part of the spectrum of autoimmune thyroid diseases (AITD). HT is a leading cause of hypothyroidism worldwide. [1–5] The diagnosis is almost certain when antibodies to thyroid peroxidase enzyme and thyroglobulin are present in the circulation in setting of hypothyroidism but the presence of diffuse lymphocytic infiltrates, lymphoid follicles with reactive germinal centers, parenchymal atrophy, and fibrosis on histology forms the basis of diagnosis of HT in truest sense. [6] HT is prevalent worldwide with prevalence rates as high as 0.3 to 1.5 per 1,000 individuals, being five to twenty times commoner in women. [7] HT is occasionally associated with development of goiter or nodule.

PTC is the most prevalent thyroid cancer worldwide with incidence as high as 7.7 per 100,000. [7] Association of HT with papillary thyroid cancer (PTC) was first reported by Dailey in 1955. [5] The prevalence of HT with PTC is higher in females so is PTC and other thyroid disorders in isolation. [8–13] The presence of chronic inflammation in HT acting as an initiating factor in carcinogenesis served as a potential explanation for the association. Thereafter there were various studies that supported this association and others that refuted it. [14–32] A Meta analysis of 8 FNA and 9 post thyroidectomy studies has revealed no clear association between PTC and HT in population based FNA studies. Even though the post thyroidectomy specimens did show a significant association between PTC and HT, these may have been subject to selection bias [6].

Molecular and Hormonal Basis of Association of PTC with HT

The relation between HT and PTC is guided by presence of thyroid antibodies and histopathological evidence of

thyroiditis in cases of PTC. [26–29, 33–39] Seminal work by Fiore et al. on HT with PTC showed high titers of thyroid antibodies (TAb) ($p<0.001$) compared to HT alone. [28] The sustained inflammatory response in HT may act as carcinogen. The concept of chronic inflammation leading to carcinogenesis is well established in other malignancies like gastric cancer, head and neck cancer, hepatobiliary cancers etc. [40] HT occasionally exhibits cytological alterations, nuclear modifications similar to those seen in PTC like RET/PTC rearrangements [41–43] and BRAF mutations [44] suggesting that the neoplastic and autoimmune disease share the same platform of molecular pathogenesis. Immune mediated receptors like TLRs and DNA repairing genes like ATM, hOGG mutations may accumulate as aberrant genetic changes in long standing HT, which serves as a precursor lesion of PTC [45].

Currently another hypothesis considered for pathogenesis of PTC in HT is solid cell nest (SCN). SCN are often small, measuring 0.1 mm or less in diameter, consisting of polygonal to ovoid cell with elongated nuclei, finely granular chromatin, and may show nuclear grooves. SCN are often found incidentally within the normal thyroid gland in the lateral lobes and may be associated with neoplastic or non-neoplastic lesions of the thyroid. [46] SCN can be misinterpreted as papillary thyroid microcarcinoma, squamous metaplasia of follicular thyroid cells, primary or metastatic squamous cell carcinoma, thyroglossal cyst, C-cell hyperplasia, and medullary microcarcinoma. The distinction between these latter lesions and SCN may usually be made on the basis of the hematoxylin and eosin (H&E) appearance, but should be confirmed by immunohistochemistry. SCN are usually negative for thyroglobulin and TTF-1 but have strongly reactivity for p63. p63 is consistently expressed in basal/stem cells of several types of epithelia and it is usually absent in partially or terminally differentiated cells. [47] Morphologic continuity between SCN and papillary thyroid microcarcinoma have been reported in view of similar BRAFV600E mutation in both the SCN and the contiguous papillary thyroid microcarcinoma suggesting a histogenetic relationship between the main cells of SCN and the papillary thyroid carcinoma. Although these findings could support a histogenetic link between SCN and papillary thyroid carcinoma, additional molecular analyses and other studies are needed to support this linkage beyond doubt [48].

Elevated levels of TSH found in hypothyroid patients with HT may stimulate follicular epithelial proliferation, thereby promoting the development of papillary carcinoma. [49–52] Fiore et.al found that TSH levels also correlated strongly with the presence of PTC in nodular HT than in nodular goiter with an odds ratio of 1.111. [28] McLeod et al. [52] conducted a systemic review that included 5,786 thyroid cancer cases in 43,032 subjects and found that elevated serum TSH confers a greater likelihood of development of thyroid cancer (odds ratio 1.87–2.83, depending on the level of TSH). A subset of studies that were adjusted for autoimmune thyroiditis did not find a similar relationship between TSH and heightened odds ratio for thyroid cancer [6].

Clinical Findings

There is no clinical finding, which starkly defines HT concurrent with PTC. Association of HT concurrent with PTC is clinically associated with decreased size of nodules in affected gland, predilection for females and a younger age group. In a study 269 participants with histologically confirmed PTC, analyzed according to the presence or absence of concurrent HT showed that HT concurrent with PTC had a greater female preponderance and were younger at presentation. PTC with HT patients tended to have smaller tumor size (1.6±1.0 cm vs. 1.8±1.5 cm) compared to patients with non-malignant HT. [102] Repplinger et.al observed that presence of a goiter was inversely associated with risk of malignancy in those patients with Hashimoto's thyroiditis. In the same study only 9 % female Hashimoto's thyroiditis patients with PTC had goiter, while 36 % female Hashimoto's thyroiditis patients without PTC had goiter ($p<0.001$) [53].

Radiological Features

HT on high-resolution ultrasonography is commonly seen as diffusely enlarged, heterogeneous, and hypervascular thyroid with micronodules, echogenic septations, and decreased echogenicity [54–57]. HT concurrent with PTC appeared more hypoechoic with well-defined margins and lobulations compared to HT. Hypervascularity is a sonographic feature considered suspicious for malignancy in nodules. [58–60] Calcifications of various types were more prevalent among malignant nodules, including microcalcifications, tiny non-specific non-shadowing bright reflectors, macrocalcifications and peripheral eggshell calcifications. Statistically significant difference was only found with microcalcifications and non-specific bright reflectors, whereas nodules that contained any type of calcification had at least a 50 % risk of being malignant. [59–62] This finding comprehends that any calcification seen in a nodule within HT should be viewed as suspicious for malignancy.

Pathological Features of HT Concurrent with PTC

Grossly, the mean diameter and size were all smaller in malignant nodules associated with HT. [53] Psammoma bodies are observed less frequently in PTC with HT compared to PTC without HT. [63] It can be a diagnostic challenge

distinguish reactive nuclear changes associated with HT from PTC arising in a background of HT in cytologic and surgical pathology specimens. The incidence of neoplasia in setting of HT by fine needle aspiration cytology is 4 %. [64] FNAC has proven its role in picking up PTC in HT with sensitivity greater than 90 % and NPV of 96 % with corresponding lower values for Hürthle cell and follicular neoplasms. The foci of reactive follicular epithelium in HT usually are adjacent to the inflammatory infiltrate and lack infiltrative edges. The nuclei are mostly round and do not exhibit overlapping and prominent intranuclear inclusions. [65–67] On the other hand, aspirates of PTC arising in association with HT usually show 2 types of cellular proliferation: tumor cell fragments devoid of percolating lymphocytes showing nuclear features of PTC and a second population of reactive follicular epithelium in association or Hürthle cell groups (round nuclei with prominent nucleoli) infiltrated by lymphocytes with focal nuclear atypia in isolation showing some but not all features of PTC [67, 68] The chances of false negative due to sampling errors do exist. Occasionally, the nuclei of the follicular cells that is associated with the lymphocytic infiltrate in HT may show clearing of the nuclear chromatin and grooves, which may be mistaken for papillary carcinoma [69].

Although limited by the lack of definitive pathology, population-based FNA studies did not find a statistically significant correlation between HT and PTC [49, 50, 70–75] whereas many of the studies of thyroidectomy specimens report a positive relationship. [53, 76–82] The average prevalence rate of PTC in patients with HT was 1.20 % in 8 FNA studies [49, 50, 70–75] of 18,023 specimens and 27.56 % in 8 archival thyroidectomy studies of 9,884 specimens. [53, 76–82] Nevertheless, thyroidectomy studies, which reported a statistically significant positive correlation, are subject to selection bias therefore FNAC forms the first diagnostic test in work up algorithm to rule out PTC [83–88].

Extent of Surgery in HT Concurrent with PTC

HT by itself is not an indication for surgery, but concurrent malignancy or the presence of goiter/nodule merits a surgical intervention. PTC is the most common thyroid malignancy with the predilection for lymphatic spread. [89] The lymphatic spread of PTC usually follows an orderly pattern with the central compartment or level VI lymph nodes being first to involve [90–92].

At diagnosis, patients of PTC with HT tend to have more limited disease, with a significantly lower frequency of extrathyroidal invasion, nodal metastases and distant metastases compared with those without HT. [93] Kim SS et.al reported that there was a negative association between the coexistence of HT with PTC and central lymph node metastasis after adjustment for age, sex, tumor size, and multifocality by multivariate logistic analysis [94].

Patients with PTC and coexisting HT have low stage disease at the time of their surgery, with a good prognosis. [93–95] PTC may be picked up earlier in setting of HT as majority of these patients may under medical follow up for hypothyroidism. Total thyroidectomy is the treatment of choice for Hashimoto's thyroiditis coexisting with papillary thyroid carcinoma especially. [79, 87, 96] The presence of PTC with HT does not alter management and extent of surgery.

Prognosis and Follow up

Investigators have proposed that PTC in setting of HT is associated with better prognosis. [76, 79, 97–101] It has been hypothesized that the favorable clinical outcome in PTC patients with concurrent HT strongly suggests that a thyroid autoimmune response may enhance or even provide an antitumor attack. The frequency of extrathyroid extension, nodal metastasis and distant metastasis is also low in this group of patients accordingly. In a study 269 participants with histologically confirmed PTC analyzed according to the presence or absence of concurrent HT showed lower incidence of lymph node metastasis at presentation (12.2 vs. 29.9 %), unifocal disease (84.5 vs. 78.7 %), and early-stage disease. Additionally, PTC with HT patients exhibited better prognosis, with lower recurrence and mortality rates, during the 62-month mean follow-up period [102].

Huang et.al [103] also observed that well-differentiated thyroid carcinoma with concomitant HT present with less aggressive clinical behaviour and low recurrence rates in 1,788 PTC patients and 209 FTC patients who underwent thyroidectomy with or without lymph node dissection. The mean tumor size of classical PTC was larger than that seen in HT concurrent with PTC group. Cancer-specific mortality was higher in classical PTC group compared to PTC with HT. Recent meta-analysis by Lee et.al has suggested a positive correlation between presence of HT and disease-free survival and overall survival in PTC. [22] Surgical complications were no higher in patients of PTC with coexistent HT, suggesting that the presence of HT does not affect the management of papillary thyroid cancers. The follow up of patients of PTC with HT is no different from those of stage and type matched PTC.

Conclusion

The causal association between HT and PTC remains elusive and larger prospective studies are needed to support or refute

this association. However based on the evidence of available literature, it would be prudent to rule out malignancy in nodular Hashimoto's Thyroiditis. The treatment of PTC associated with HT is no different from that of stage and type matched PTC and HT concurrent with PTC have a better prognosis compared to age and stage matched PTC alone.

Conflicts of interest The authors declare that there is no conflict of interest.

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