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The Relationship Between Hashimoto's Thyroiditis and Papillary Thyroid Carcinoma: Trying to Explain the Paradox.

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ABSTRACT

Background: *Hashimoto's thyroiditis (HT) and papillary thyroid microcarcinoma (PTMC) often coexist. Their relationship is paradoxical and unclear.*

Materials and Methods: *This retrospective study reviews 1,509 thyroidectomies from 2018–2025, focusing on PTMC cases compared with benign thyroidectomy controls to assess the link between PTMC and HT.*

Results: *37% of PTMC cases have HT, versus 27% of controls. The odds ratio (OR) for PTMC among HT patients is 1.6 (95% CI: 1.046-2.46; $p = 0.03$), indicating an increased risk. The risk is higher in euthyroid HT, with 63% prevalence in PTMC vs. 12% in controls. The OR for PTMC in euthyroid HT is 13 (95% CI: 4.53-37.04; $p < 0.0001$). PTMC occurs at a younger age with HT (40 vs. 44; $p < 0.05$). HT with PTMC reduces lymph node metastasis (LNM) without affecting tumor size. The tumor immune microenvironment (TIME) differs: the immune-inflamed "hot" subtype is more common in HT, while the immune-desert (ID) subtype is more common in non-HT cases. The "hot" type is immunosuppressive and is associated with increased lymph node metastasis, particularly in non-HT-associated PTC.*

Conclusion: *Euthyroid HT is associated with increased PTMC risk, likely arising early in chronic inflammation before autoimmunity. The dominant "hot" TIME subtype appears immunosuppressive, suggesting a potential role for immunotherapy in PTC.*

Keywords: *Hashimoto's thyroiditis; Papillary thyroid carcinoma; Papillary thyroid microcarcinoma; Tumor immune microenvironment; Thyroid-stimulating hormone; Thyroid peroxidase antibodies.*

Introduction

Hashimoto's thyroiditis (HT) and papillary thyroid carcinoma (PTC) are common in women and frequently co-occur, although their relationship remains complex. HT is associated with an increased risk of PTC, yet PTC in patients with HT tends to exhibit slower growth and a more favorable prognosis [1,2].

Autoimmunity and cancer were traditionally viewed as opposing processes: autoimmunity results from a loss of immune tolerance to self-antigens, whereas cancer progression relies on increased immune tolerance that enables tumor immune escape. Recent immunological research has shown that these processes are interconnected through immune checkpoint pathways, particularly the programmed cell death protein 1 (PD-1)-PD-L1 axis and regulatory T cells (Tregs) [3]. These checkpoints suppress T-cell activation by promoting Tregs and limiting self-reactive effector T cells, thereby maintaining immune tolerance [4]. PD-1 is primarily expressed on immune cells, while PD-L1 is found on both immune and non-immune cells, including epithelial cells. Tumor cells can exploit PD-

L1 overexpression to evade immune surveillance and facilitate unchecked growth [5].

Disruption of the PD-1/PD-L1 pathway, through genetic polymorphisms or prolonged immune exhaustion during chronic inflammation, can impair immune tolerance and contribute to autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, and type 1 diabetes [6]. Although a direct role for the PD-1/PD-L1 pathway in HT has not been definitively established, variable expression of PD-1 and PD-L1 has been reported in HT, with lower levels observed in vivo than in vitro. Notably, immune checkpoint inhibitor therapy targeting PD-1/PD-L1 is associated with a high incidence of autoimmune thyroid disease [7,8]. An intact PD-1/PD-L1 pathway may contribute to the persistence of HT and limit early remission [7,9,10].

Autoimmune thyroiditis develops along a morphological and functional spectrum. Early disease is characterized by a less destructive chronic inflammatory phase, while later stages involve extensive tissue damage and oncocytic metaplasia [11,12]. Early HT is often associated with lower thyroid-stimulating hormone (euth-TSH) levels and lower titers of thyroid peroxidase (TPO) antibodies [12]. This phase may be sustained by a functional PD-1/PD-L1 system, whereas chronic immune activation eventually leads to pathway exhaustion, increased autoantibody production, and hypothyroidism.

Histologically, HT is marked by lymphoplasmacytic infiltration and secondary lymphoid follicle formation, changes that are indistinguishable from reactive lymphocytic thyroiditis. The diagnosis of HT becomes clear once these features are accompanied by autoantibody production, destructive changes, and elevated TSH levels. While autoantibodies are present in approximately 95% of cases, early stages may exhibit normal TSH due to compensatory thyroid function and are often identified incidentally during fine-needle aspiration or thyroidectomy performed for other indications [13].

To further explore the association between HT and PTC, we conducted an observational study of histologically confirmed HT cases with papillary thyroid microcarcinoma (PTMC). Serum TPO antibody and TSH levels were analyzed and compared with those of a benign control group, and histological sections were reviewed to characterize the local immune response. PTMC was selected because of its high diagnostic frequency at our institution [14], its stronger association with HT [15], and its capacity to elicit localized immune responses comparable to those observed in established PTC.

Material and Methods

PTMC cases diagnosed incidentally or preoperatively in complete or partial thyroidectomies performed between 2018 and 2025 were retrieved from the archives of the Department of Laboratory Medicine and Pathology at Security Force Hospital, Riyadh, Saudi Arabia. An equal number of age- and sex-matched controls was selected from the same time frame as consecutive benign thyroidectomies for comparative analysis. Each group was divided into two subgroups based on the presence or absence of histologically confirmed HT. TPO and TSH levels were measured as part of the initial workup prior to initiation of medical or surgical therapy. TSH levels were classified as euthyroid (4.0 mIU/L) or hypothyroid (<4.0 mIU/L). The prevalence rates of HT, TPO positivity, and TSH levels are reported for each group in Table 1.

The relationship between histologically confirmed HT, TPO positivity, and hypothyroid versus euthyroid TSH levels (hypo-TSH vs. euth-TSH) with the risk of developing PTMC was analyzed and compared independently. The strength of the association between HT, TPO positivity (>34 IU/ml), TSH levels, and the development of PTMC was reported as an odds ratio (OR) in Table 1.

Pathological features associated with aggressive behavior, including tumor size, morphological subtype, multiplicity, bilaterality, margin involvement, and central lymph node metastasis, were documented and compared between the groups (Table 2). The number of lymph nodes identified in each group and subgroup was recorded and compared.

The tumor immune microenvironment type (TIME) surrounding PTMC on histological sections is classified into three categories based on the level of cell infiltration within and around the tumor. The immune desert (ID) group has fewer lymphocytes both within and outside the tumor. The immune-excluded (IE) group shows clear lymphocyte infiltration around the tumor but few within it. The immunoinflammatory (Inf) group exhibits extensive lymphocytic infiltration of the tumor [16]. These categories are linked to the presence or absence of HT, tumor size, and lymph node metastasis (Table 4).

The SPSS program was used for statistical analysis and data management. A two-tailed chi-square (χ^2) test was used to assess differences in proportions, while a two-tailed t-test was used to compare means, such as age and tumor size.

Results

Study population

This study includes 195 consecutive cases in the PTMC group diagnosed between 2018 and 2025, among 1,509 partial or complete thyroidectomies. The patients' ages ranged from 20 to 89 years, with a mean age of 43.5 ± 12. The cases consisted of 166 females and 29 males, with an F/M ratio of 6:1.

An age- and sex-matched control group included an equal number (195) of consecutive cases of benign partial or total thyroidectomies from the same time frame, all without a prior history of thyroid cancer. This group comprised 163 females and 32 males, resulting in a female-to-male ratio of 5:1. The patients' ages ranged from 15 to 80 years, with a mean age of 43.5 ± 12.

The prevalence of HT, preoperative TPO positivity, and TSH levels in the PTMC group compared to the control group

Findings are summarized in Table 1.

Table 1. Prevalence of HT, high serum TPO, and euth-TSH in PTMC vs. the control group.

Variable	HT (PTMC)	HT (Control)	Non-HT (PTMC)	Non-HT (Control)
No. cases	72/195 (37%)	52/195 (27%)	123/195 (63%)	143/195 (73%)
TPO Positive	45/57 (79%)	41/47 (87%)	21/80 (26%)	12/96 (13%)
Euth-TSH	27/43 (63%)	6/52 (12%)	106/119 (89%)	104/143 (72%)
Age	40.0 ± 10	44 ± 9	46 ± 12	44 ± 13

The study involved 390 cases, evenly split between the PTMC and benign (control) groups. A total of 124 cases had a morphologically confirmed diagnosis of HT, including 72 PTMC and 52 benign cases. The non-HT group comprised 266 cases, including 123 PTMC and 143 benign lesions.

Preoperative TPO records were accessible for 137 (70%) cases in the PTMC group and 134 (69%) in the control group. Preoperative TSH records were available for 162 cases (83%) in the PTMC group and for all cases (100%) in the control group.

The prevalence of HT among PTMC cases is 37%, which is notably higher than the 27% observed in benign cases. As a result, the odds ratio (OR) for developing PTMC with HT presence is 1.6 (95% CI: 1.046–2.46; $p = 0.03$), indicating a statistically significant increase in risk.

Hypothyroid TSH levels are found in 65% of the entire HT population and 20% of the non-HT population. The difference is statistically significant at $p < 0.0001$ ($\chi^2 = 139.25$).

PTMC is more commonly seen in euthyroid HT. Sixty-three percent of HT cases with PTMC are euthyroid, compared to only 12% of benign HT cases. As a result, euthyroid HT cases are at a greater risk of developing PTMC, with an odds ratio of 13 (95% CI: 4.53–37.04; $p < 0.0001$).

Notably, HT associated with PTMC was diagnosed at a significantly younger age than HT in the control group ($t = 2.050$; $p = 0.04$).

Pathological features of aggressive behavior in PTMC associated with HT, TPO autoantibody positivity, and TSH levels

The results are presented in Tables 2A, 2B, and 2C.

Table 2A. Pathological features of aggressive behavior associated with HT

Parameter	HT	Non-HT	P value
Tumor size	5.5 ± 2.8	5.3 ± 2.6	0.664
Involved margin	13/72 (18%)	31/123 (25%)	0.250
Multiplicity	28/72 (39%)	40/123 (33%)	0.369
Bilaterality	20/72 (28%)	26/123 (21%)	0.360
No. lymph nodes	4.7 ± 7.9	1.9 ± 4.1	0.001
Positive lymph nodes	3/68 (4.4%)	14/101 (14%)	<0.05

Table 2B. Pathological features of aggressive behavior related to TPO positivity

Parameter	Positive TPO	Negative TPO	P value
Tumor size	5.8 ± 2.6	5.4 ± 2.6	0.434
Involved margin	14/33 (42%)	52/104 (50%)	0.449
Multiplicity	22/64 (34%)	26/71 (37%)	0.786
Bilaterality	16/64 (25%)	17/71 (23%)	0.887
No. lymph nodes	4.4 ± 8.0	2.0 ± 2.6	<0.02
Positive lymph nodes	6/60 (10%)	9/58 (16%)	0.152

Table 2C. Pathological features of aggressive behavior linked to TSH level

Parameter	Hypo-TSH	Euth-TSH	P value
Tumor size	5.5 ± 2.8	5.3 ± 2.6	0.656
Involved margin	10/52 (19%)	33/149 (22%)	0.659
Multiplicity	14/42 (33%)	53/149 (36%)	0.789
Bilaterality	9/42 (21%)	38/149 (26%)	0.589
No. lymph nodes	4.1 ± 9.7	2.7 ± 4.3	0.165
Positive lymph nodes	4/35 (11%)	13/130 (10%)	0.703

There is no significant difference among subgroups in tumor size, focality, bilaterality, or margin involvement; however, PTMC tends to be multifocal and bilateral, with less margin involvement in HT.

The presence of HT, TPO positivity, and TSH levels has no effect on tumor burden or margin status. The only notable differences are in the number of lymph nodes identified and the LNM rate.

A total of 17 out of 169 cases of LNM were reported, with the majority (82%) involving only the central lymph nodes. Lateral lymph node involvement was seen in just 3 cases (18%). The HT subgroup had a higher average number of harvested lymph nodes (4.7) than the non-HT group (1.9). Despite this, the HT group had significantly fewer lymph node metastases (LNM; 4.4% with HT versus 14% in the non-HT group).

There is also a trend, though not statistically significant, for PTMC associated with non-HT to reach a margin more often than PTMC associated with HT (25% vs. 18%).

TPO positivity and hypothyroidism do not influence lymph node metastatic status in PTMC.

Tumor immune microenvironment types (TIME) and their distribution in HT and non-HT groups

There are statistically significant differences in the distribution of TIME between PTMC cases linked to HT and those not linked to HT ($\chi^2 = 44.65$; $p < 0.0001$). In HT-associated cases, the immune-inflamed subtype is most common (64%), followed by immune-excluded (25%) and immune desert (11%) (Figure 3, 2, and 1, respectively). Conversely, PTMC cases not linked to HT mainly show the immune desert subtype (51%) (Figure 1), with immune-excluded and immune-inflamed types at 30% and 19%, respectively (Figure 2 and Figure 3). Overall, immune-inflamed subtypes are present in 36% of PTMC cases regardless of HT status (Table 3).

Table 3. Distribution of TIME subtypes among PTMC cases with and without HT

Variables	ID	IE	Inf	Total
HT	8 (11%)	18 (25%)	46 (64%)	72
Non-HT	62 (51%)	36 (29%)	24 (20%)	122
Total	70 (36%)	54 (28%)	70 (36%)	194

The influence of TIME subtypes on tumor size and lymph node metastatic status

The results in Table 4 show that the TIME subtype ID ("cold") correlates with smaller tumor sizes, fewer harvested lymph nodes, and lower rates of LNM. Conversely, the "hot" subtype is associated with larger tumors, more harvested lymph nodes, and a higher incidence of LNM. The IE subtypes are intermediate, positioned between these two groups (Table 4A).

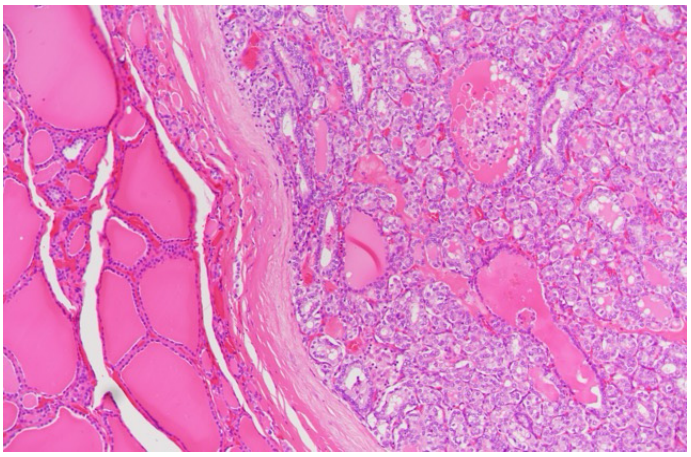

Figure 1. *H&E-stained section (10×) from a case of PTC showing no inflammatory infiltrate, either within or around the tumor, consistent with an immune-desert (ID) "cold" microenvironment.*

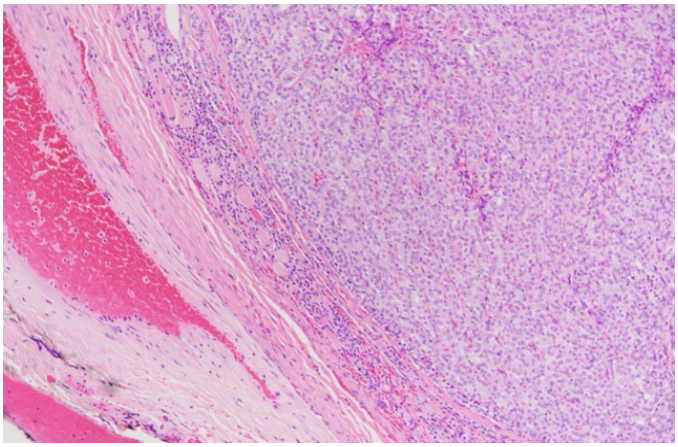

Figure 2. *H&E-stained section (10×) from PTC showing dense inflammatory infiltrate only around the tumor, indicating an immune-excluded (IE) microenvironment.*

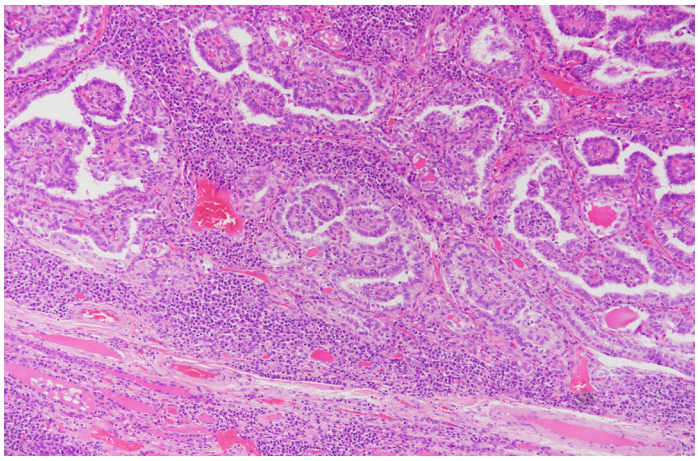

Figure 3. *Immune-inflamed (Inf) "hot" pattern in PTC from an HT case, showing dense inflammatory infiltrate within the tumor.*

Table 4A. Tumor size and prevalence of lymph node metastasis of PTMC across TIME subtypes

Variable	ID	IE	Inf	P value
Tumor size	4.7 ± 2.5	5.2 ± 2.5	6.2 ± 2.6	<0.01
No. of lymph nodes	1.2 ± 2.1	2.4 ± 3.1	5.0 ± 8.8	<0.001
Lymph node metastasis	1	6	9	<0.05

When comparing PTMC cases with and without HT, the "hot" (Inf) pattern, which is more common in HT than in non-HT (68% vs. 20%), was strongly associated with a higher rate of LNM in non-HT cases ($p < 0.0001$; Fisher's exact test). There was no difference in the ID pattern between the HT and non-HT groups with respect to the number of lymph nodes removed or the incidence of LNM. However, in non-HT cases, the IE pattern showed a noticeable trend toward increased LNM, although this was not statistically significant (Table 4B).

Table 4B. Prevalence of lymph node metastasis across TIME subtypes in HT vs. non-HT

Variable	ID	IE	Inf
HT	0/7	0/17	3/44 (7%)
Non-HT	1/50	6/30	6/20 (30%)
P value	1.000	0.074	<0.0001

Discussion

Thyroid diseases, both benign and malignant, are common in Saudi Arabia. Thyroid cancer ranked seventh globally and third nationally in 2022, with incidence rising from fewer than 2 to 14 cases per 100,000 over the past three decades. Mortality rates have nearly tripled, particularly among males [17]. Hypothyroidism, most commonly caused by Hashimoto's thyroiditis (HT), is also highly prevalent, affecting 10.3%–25.5% of the population, with a mean prevalence of 17.4%, significantly exceeding the global average of 7.5% [18,19].

Because papillary thyroid carcinoma (PTC) and HT frequently coexist, their etiological and prognostic relationship has attracted considerable research interest [20]. HT is a chronic autoimmune inflammatory disorder characterized by lymphoplasmacytic infiltration, fibrosis, and autoantibody production. Proinflammatory microenvironmental changes, angiogenesis, immune dysregulation, and hormonal alterations may interact with genetic events, promoting carcinogenesis and influencing tumor behavior.

Although studies evaluating the association between HT and PTC have yielded mixed results, most evidence supports a significant association, with HT occurring more frequently in PTC than in benign thyroid disease [1,21,22]. HT has also been linked to multifocality, bilaterality, reduced extrathyroidal extension, fewer lymph node metastases, and improved recurrence-free survival [22]. This paradox suggests that while HT increases the risk of PTC, it may also confer a less aggressive tumor phenotype.

Data from the Middle East remain limited. A Saudi study found no association between follicular epithelial dysplasia, autoantibody positivity, or hypothyroidism in HT and PTC [23]. Similarly, an Egyptian institutional study reported no increased risk of PTC in HT, although HT was associated with tumor multiplicity without affecting lymph node metastasis or extrathyroidal extension [24]. In the Middle East, PTC has been shown to be associated with PD-L1 overexpression, BRAF V600E mutations, and poor prognosis [25].

This retrospective case-control study examined the association between HT, including serological (TPO) and functional (TSH) parameters, and papillary thyroid microcarcinoma (PTMC) in a Saudi population. While no association was observed between TPO positivity and PTMC, HT was significantly associated with PTMC (OR = 1.6). Notably, PTMC in HT patients was strongly associated with euthyroid TSH levels (OR = 13; 95% CI: 4.53-37.04; $p < 0.0001$). This inverse relationship between HT and hypothyroidism contrasts with prior studies showing increased PTC risk with elevated TSH levels [26,27]. Importantly, TSH levels in our cohort were measured at diagnosis before thyroxine therapy, unlike in previous studies [28].

Our findings suggest that PTMC develops during the early chronic inflammatory phase of HT, before progression to overt autoimmune destruction. This is supported by the younger age at diagnosis and preserved thyroid function in HT-associated PTMC. These observations align with proposed mechanisms in which chronic inflammation promotes carcinogenesis prior to immune-mediated tissue destruction [29]. Elevated TPO levels in this context may reflect early innate immune activation preceding adaptive autoimmunity [30].

Genetic evidence further supports inflammation-driven carcinogenesis. Regional gene-expression studies indicate that PTC arising in HT is more closely associated with oxidative stress- and inflammation-related oncogenic pathways than with autoimmunity per se [31]. Similarly, RET/PTC rearrangements were not associated with HT-related PTC, suggesting alternative oncogenic mechanisms [32].

In our cohort, HT did not significantly affect tumor size but was associated with higher rates of multifocality and bilaterality, reduced surgical margin involvement, and significantly lower lymph node metastasis. These findings are consistent with prior reports [1,21,22]. To explore potential mechanisms, we analyzed the tumor immune microenvironment (TIME).

Using morphological classification, immune-desert (ID) and immune-excluded (IE) patterns were associated with smaller tumors and fewer lymph node metastases than immune-inflammatory ("hot") tumors, contrary to traditional assumptions [33]. These findings are better explained by the cancer immunity cycle model, in which ID represents early immune recognition, IE reflects partial immune penetration limited by fibrosis, and the "hot" pattern corresponds to immune exhaustion and checkpoint activation [34].

While the "hot" pattern was associated with higher overall lymph node metastasis, HT-associated "hot" tumors showed significantly lower metastasis than non-HT cases. This supports observations that HT-related PTC exhibits a more active antitumor immune response [16], despite contradicting reports of increased metastasis. The differential behavior likely reflects variations in the proportions of cytotoxic T cells and regulatory T cells, as well as in immune checkpoint expression. In HT, reduced PD-1 expression and preserved immune surveillance may limit tumor progression, whereas non-HT tumors exhibit greater immune evasion via PD-1/PD-L1 signaling [4,33].

Overall, our findings support a model in which chronic inflammation initiates PTMC during early HT, while subsequent autoimmune processes modulate tumor aggressiveness. This dynamic interplay between inflammation, immunity, and cancer aligns with established phases of cancer immunoediting: elimination, equilibrium, and immune escape [35].

Conclusion

In conclusion, Hashimoto's thyroiditis (HT), an autoimmune condition, significantly increases the risk of developing papillary thyroid carcinoma (PTC), particularly among young, euthyroid women. Paradoxically, HT is also associated with less aggressive tumor characteristics, including a lower incidence of lymph node metastasis. These seemingly contradictory observations likely reflect the complex, not yet fully understood interplay among chronic inflammation, autoimmunity, and tumor immune surveillance. Notably, the predominance of a "hot" immune microenvironment in PTC, regardless of the presence of HT, and the consequent reduction in tumor immunogenicity, suggest that selected cases of advanced or complicated PTC may benefit from immunotherapeutic approaches.

Human Ethics Declaration

This study received approval from the research committee at Security Force Hospital in Riyadh, in accordance with the Saudi Arabia National Committee of Bioethics (NCBE), under accreditation number H-01-R-069.

Author contributions

Imad Abdien El Hag: Conceptualization, statistical analysis, histological slide review, and manuscript writing.

Khalid Aburas: Data collection and preliminary data categorization.

Shuaa Asiri: Manuscript Editing.

Conflicts of Interest and Funding

The authors declare no conflict of interest and received no specific funding for this work.

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