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# Papillary Thyroid Carcinoma Intertwined with Hashimoto's Thyroiditis: An Intriguing Correlation

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## Abstract

Illustrating the ancient link connecting inflammation with cancer, the correlation of papillary thyroid carcinoma (PTC) with Hashimoto's thyroiditis (HT) has long been pursued as intersection of autoimmunity-induced chronic inflammation and tumor-induced immunity. The dramatic rise of the incidence of PTC over the last decades—the main culprit for “thyroid cancer (TC) epidemic”—parallels the increasing incidence of HT, potentially reflecting a pathogenetic link that could be harnessed in diagnostics and therapeutics. Prompted by this perspective, in the present chapter, we dissect the hitherto elusive interrelationship of PTC with HT, focusing on four issues: firstly, an unresolved conundrum is whether PTC emerges due to or notwithstanding immune response or mirrors the “tumor defense-induced autoimmunity.” Secondly, the interrelationship of HT with PTC may be merely epiphenomenon of selection bias inherent in thyroidectomy series. Thirdly, the impact of HT on coexistent PTC is equivocal—host protective versus tumor protective. Fourthly, translating serum concentrations of thyroid autoantibodies and thyroid-stimulating hormone (TSH) into predictive and prognostic PTC biomarkers dichotomizes, till now, the researchers. In the era of precision medicine, illuminating whether HT precipitates PTC or *vice versa* is awaited with anticipation in order to refine the preventive and therapeutic policy counteracting “TC epidemic.”

**Keywords:** papillary thyroid carcinoma, hashimoto's thyroiditis, anti-thyroglobulin autoantibodies, anti-thyropoxidase autoantibodies, thyroid-stimulating hormone

## 1. Introduction

Initially reported by Dailey et al. in 1955, the correlation of papillary thyroid carcinoma (PTC)—the most common thyroid cancer (TC) histotype—with Hashimoto's thyroiditis (HT) [1] has long been pursued, rekindling the ancient link between inflammation and cancer [2]. Bearing in mind the rising incidence of PTC over the last decades [3], establishing causality between PTC and HT—an issue highly contested—could lay the groundwork for a preventive policy. Moreover, harnessing the interrelationship of PTC with HT could refine therapeutics with respect to PTC. The present chapter dissects the correlation of PTC

with HT, delving into a strongly insinuated immunological link. A comprehensive review of current literature emphasizes on the bewildering clinical significance of the interrelationship of PTC with HT. The intriguing predictive and prognostic value of serum concentrations of thyroid autoantibodies and thyroid-stimulating hormone (TSH) in the context of PTC coexistent with HT paints a more nuanced and sophisticated picture.

## **2. Tailoring the treatment of PTC: where does coexistent HT stand?**

Thyroid cancer (TC) is the most common endocrine malignancy [4], though comprising only 2.1% of global cancer burden [5]. It is estimated that 52,070 new TC cases will occur in 2019 in the United States, while 2170 patients will die of this cancer type [6]. Derived from follicular epithelial cells, PTC constitutes the most common TC subtype in iodine sufficient areas, accounting for 85% of differentiated TC (DTC) [7] and 70–80% of TC [8]. In light of the interface between “TC epidemic” and “epidemic of diagnosis,” a true increase of the incidence of PTC due to environmental, hormonal, and lifestyle risk factors appears to be merged with overdiagnosis of subclinical disease owing to meticulous screening [3, 9–11].

The indolent nature of PTC imposes a paradigm shift from ameliorating 10-year survival rates exceeding 90% to eliminating the recurrence incidence that hovers at 15–30% [12]. Individualization of therapeutic approach is deemed to confront the emerging challenges [13]. Seminal studies [4, 14, 15] recently illuminated the “dark matter” of the previously unidentified driver genetic events in 96% of PTC [4], being translated into molecular-based risk-adapted therapeutic strategies [7]. Although surgery is the cornerstone of treatment of PTC, a tailored approach with respect to the extent of thyroidectomy and lymph node dissection, the radioiodine ablation, and the management of radioiodine-refractory recurrent/metastatic disease has been endorsed [7].

Provided that the clinical relevance of the increasingly reported interrelationship of PTC with HT is clarified, the incorporation thereof in current PTC risk stratification systems may empower a personalized treatment. This perspective is anticipated to build on accomplishing a fine-tuned balance in terms of decision-making concerning PTC, precluding both overestimating an innocent disease and ignoring a metastatic potential.

## **3. HT at a glance**

HT, originally designated as “struma lymphomatosa” by Dr. Hakaru Hashimoto in 1912 [16], is the most common autoimmune thyroid disease and the most common cause of hypothyroidism in iodine sufficient areas, showing a worldwide annual incidence varying from 0.3 to 1.5 cases per 1000 individuals [17]. An insightful approach concerning the multifactorial etiology of HT has been proposed by Weetman et al.: aligned in a way reminiscent of the wholes of the Swiss cheese are genetic factors acting as susceptibility loci—major histocompatibility human leukocyte antigen (HLA) genes, immunoregulatory genes, thyroid specific genes—environmental factors—excess iodine intake, viral infections, stress, endocrine disruptors—as well as non-modifiable intrinsic factors—female sex, parity, age. Traversed by a hypothetical arrow, this conceivable line translates in a catastrophic event [18].

The histopathologically confirmed HT is characterized by diffuse lymphocytic infiltrate, formation of lymphoid follicles with germinal centers within normal

thyroid tissue [19], and, potentially, atrophy of parenchymal tissue gradually replaced by fibrous tissue [20]. The identification of the autoantibodies hallmark of HT in 1936 [21] paved the way for Rose and Witebsky to designate HT as the archetype of autoimmune destructive disorders [22]. Whereas the pathogenesis of HT is unclear, crucial is considered the imbalance between T-helper (Th)2 cells—Th CD (cluster of differentiation)4+ cells credited with stimulation of B cells, which in turn produce thyroid autoantibodies- and Th1 cells-cytotoxic Th CD4+ cells directly attacking the thyroid follicular cells. This concept has been refined by the imbalance between Th17 cells and Th cells producing mainly IL-17, involved also in carcinomas- and T regulatory (Treg) cells-Th CD4+ cells deemed to halt the immune response [23]. Especially, an increased TH17/Treg ratio ascribed to both enhancement of TH17 expression and decrease of Treg is involved in the pathogenesis of HT [24]. Incriminated for the depletion of thyrocytes in HT is principally the autocrine/paracrine Fas-/Fas ligand (FasL)-induced extrinsic apoptotic pathway [24, 25].

#### **4. Rationality in the investigation of the interrelationship of PTC with HT**

Apart from the well-established connection of HT with thyroid lymphoma [26], which is beyond the scope of the present chapter, the association of TC with HT concerns almost exclusively the PTC [27], alluding to a discriminating, though unknown, pathogenetic link.

Since PTC is conceived as the main culprit for the explosive rise of TC incidence [3], the hypothesis that the increasing incidence of HT hastens the “TC epidemic” is appealing. Considering that the inflammation has been envisaged as the “seventh hallmark of cancer” [28], the autoimmunity-induced inflammatory milieu [29] merits further interrogation as the missing piece in the puzzle of the interrelationship of PTC with HT.

An alternative explanation that cannot be ruled out is that third extraneous variables actually cause the coexistence of PTC with HT. Indeed, both PTC and HT are precipitated by an interplay among genetic factors and environmental influences most of which are shared by the two entities. Emphasis is placed on risk factors implicated in the pathogenesis of both PTC and HT, such as female predominance, excess iodine intake, and exposure to radiation [30–34], implying a spurious correlation.

Nonetheless, a common origin of PTC and HT from cancer stem cells expressing p63 proteins—homologs of p53 proteins postulated to regulate squamous stem cell commitment—has been suggested. In fact, the cancer stem cells constitute pluripotent cells deemed to remain undifferentiated or undergo benign squamoid and glandular maturation or be differentiated to follicular epithelial cells, harboring the potential to elicit both PTC and HT [35, 36].

The interrelationship of PTC with HT spurs a realm of intense research, principally in four respects. Firstly, the pathogenetic link between HT and PTC remains elusive; however, accumulative evidence suggests that these two entities are immunologically linked [29]. Secondly, some authors argue that this interrelationship is merely epiphenomenon of selection bias inherent in studies encompassing surgical series [37, 38]. Thirdly, equivocal—favorable versus unfavorable—is the impact of HT on the prognosis of concurrent PTC [39–48]. Finally, the translation of the serum concentrations of thyroid autoantibodies [49–56] and thyroid-stimulating hormone (TSH) [55, 57–63] into predictive and prognostic PTC biomarkers incites a perpetual conflict.



## **5. Exploring the immunological link between PTC and HT**

Compelling evidence insinuate that the PTC and the HT represent two extremes in the continuum of immune response. In cancer, dominant is an anti-inflammatory response dictated by cancer cells per se, counteracting the antitumor immune surveillance. Quite the contrary, an overactivated inflammatory response owing to breakage of self-tolerance attacks host tissue cells, resulting in tissue damage in the context of autoimmune diseases. Despite the fundamental differences between the tumor microenvironment and the autoimmune milieu, certain parallel aspects of these two landscapes have been recognized [64]. For instance, the macrophages (M) and the neutrophils (N)—cells of myeloid origin—are encountered in both cancer and autoimmunity that act as well-coordinated partners to orchestrate the innate immune attack. Showing plasticity, these cells transition from proinflammatory M1/N1 polarization, devoted to kill pathogens or cancer cells, to anti-inflammatory M2/N2 polarization, dedicated to repair tissue damage and promote angiogenesis. A shift toward M2 macrophage polarization is a core component of tumor microenvironment, observed in autoimmune milieu as well, providing a hint to the interface thereof. Furthermore, supportive of the tumor-promoting M2 macrophage polarization is the local hypoxic milieu inherent in both autoimmune and cancerous diseases [64].

The elucidation of the continuum of immune response could provide insights into the pathogenetic background of the coexistence of PTC with HT. Given that the macrophage phenotype M2 is considered tumor-promoting contrary to the antitumor effect of M1 phenotype, an appealing hypothesis connecting PTC with HT is derived from the intrathyroidal immune profiling of euthyroid HT conducted very recently by Imam et al. [65]. The immune infiltrate in euthyroid HT proved to contain low count of natural killer (NK) cells, facilitating the differentiation of the macrophage phenotype M0 to the M2 phenotype, which in concert with the observed low count of M1 macrophages may interpret the higher risk of PTC inherent in euthyroid HT [65].

Interestingly, overexpression of Toll-like receptors (TLR)—cell surface receptors credited with recognition of pathogen-related molecules, crucial for activation of innate and adaptive immunity—is detected immunohistochemically in human thyrocytes surrounded by immune cells in all patients with HT. The high basal TLR3 mRNA levels observed in PTC, reinforcing the shared immunological landscape, are consistent [66, 67].

Dissecting the interface of HT with PTC is expected to unveil novel targets for immunomodulation. For instance, triggering the innate immunity via the TLR5 agonist flagellin, being already in clinical trials as inducer of NK activation [68], could be interrogated as a modality to reverse the M2 macrophage phenotype in PTC coexistent with HT.

In pursuit of the immunological link connecting PTC with HT, three hypotheses, rather interrelated, shape a conceptual framework outlined below.

### **5.1 Thyroid malignancy develops despite immune response in the context of HT**

Manifold mechanisms have been proposed to underlie the escape of PTC cells from immune response in the context of autoimmunity: (i) the ability of PTC cells to manipulate the expression of immune-regulatory cytokines, editing the immune response; (ii) the enhancement of Treg known to suppress the NK cell effector functions, mainly the cytotoxicity; and (iii) the promotion of expression of specific surface molecules facilitating tumor development and growth, such as the membrane-bound transforming growth factor b (TGFb), histocompatibility antigen, class 1, G (HLA-G), FasL, and B7 homolog 1(B7H1) [28].

Moreover, the interrelationship of PTC with HT may empower the escape of cancer cells from immune surveillance, consolidating the dogma that “cancer is a wound that never heals since tumor cells hijack the wound healing machinery for their own gain” [69]. In fact, a recently discovered “unexpected player”, the T cell double negative (DN) CD4(−) CD8(−), expressed both in PTC and in thyroid autoimmunity, downregulates the proliferation of activated T effector cells and the cytokine production, fostering an immunosuppressive microenvironment [70]. Favoring immune tolerance, the FOXP3+ Treg cells—crucial players of thyroid autoimmunity [71]—are encountered also in PTC [70]. The dendritic cells (DCs), beyond governing the autoimmune milieu, are also expressed in PTC, being responsible for the expansion of FOXP3+ Treg cells, allowing the tumor immune evasion and, thus, enabling the PTC progression [72].

## 5.2 Thyroid malignancy develops owing to thyroid autoimmunity

The first detection of lymphocytes in neoplastic tissues by Virchow in 1863 [73] paved the way for the endorsement of chronic inflammation as a precipitating factor for certain cancer types. In that respect, thyroid gland could be conceived as an intersection of HT-induced chronic inflammation and cancer; however, a causal relationship is yet to be defined. In light of the cancer-related inflammation (CRI), the concurrence of PTC with HT might reflect either the malignant transformation ascribed to an autoimmunity-induced chronic inflammatory milieu (extrinsic pathway) or the inflammatory response to tumor (intrinsic pathway) [74].

The perpetually overactive immune response in the context of HT initiates an inflammatory vicious cycle with the potential to gear the journey of normal cells toward malignancy, rendering the interrelationship of PTC with HT the epitome of the extrinsic pathway of CRI [74].

Central in the extrinsic pathway is the “smoldering inflammation,” an ungoverned inflammatory milieu orchestrated by immune/inflammatory cells, involving macrophages, immature DCs, and mast cells, expressing a myriad of cytokines, chemokines, and growth factors, such as interleukin (IL)-1b, tumor necrosis factor  $\alpha$  (TNF $\alpha$ ), IL-6, (C-C motif) ligand 2 (CCL2)/monocyte chemoattractant protein 1 (MCP-1), CXC chemokine ligand (CXCL8)/IL-8, vascular endothelial growth factor (VEGF), as well as reactive oxygen species (ROS) and reactive nitrogen species (RNS), spurring tissue damage, neo-angiogenesis, and tissue remodeling [75, 76]. Implicated in this milieu is the hypoxic microenvironment, inherent in both PTC and HT, favoring the progression of tumor, reinforcing, among others, the neo-angiogenesis and the shift of metabolism toward anaerobic glycolysis [64].

Overexpression of cyclooxygenase-2 (COX-2)—an enzyme involved in initiation [77] and progression of thyroid tumors [78]—and inducible nitric oxide synthases (iNOS), key elements of CRI, has been observed in epithelial cells of lymphocytic thyroiditis, follicular adenoma, and PTC contrary to the absence or the limited expression thereof in normal thyroid epithelium, potentially linking carcinogenesis to autoimmunity [79].

Intertwined with the extrinsic pathway is the intrinsic pathway: genetic alterations caused by DNA damage induced by the “smoldering inflammation” [80] trigger a proinflammatory transcriptional program [74]. For instance, the oncogene RAS is involved in the induction of chemokine CXCL8 [75], an inflammatory mediator of both cancer [75] and autoimmunity [64]. Moreover, phosphatase and tensin homolog (PTEN) mutation, a key element of the oncogenic phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) pathway, leads to upregulation of hypoxia-inducible factor-1 (HIF1), which, in turn, upregulates the CXC chemokine receptor 4 (CXCR4) [75], well-recognized player of autoimmunity [81]. Accordingly, the observed activation of the PI3K/AKT pathway in HT, PTC, and HT coexistent with PTC contrary to the absence of activation thereof in normal follicles is rational [82].

Illustrating the common molecular background shared by PTC and HT, the rearranged during transfection (RET)/PTC rearrangements—landmarks of PTC—are detected in 95% of HT [83]. Moreover, the RET/PTC1 rearrangement has been detected more frequently in PTC coexistent with autoimmunity than PTC alone (31% versus 13%, respectively) [84]. The inflammatory milieu fosters the genesis of RET/PTC rearrangements either via secreting ROS and RNS [85]—the main culprit for mutagenic-mediated DNA damage [2]—or sustaining the survival of thyroid cells that harbor RET/PTC rearrangements.

The oncogenic RET/PTC-RAS-BRAF-mitogen-activated protein kinase (MAPK) cascade [74] may connect the oxyphil cell metaplasia of HT with PTC, considering the enhancement of the expression of RET, nuclear RAS, and extracellular signal-regulated kinases (ERKs)—core components of MAPK cascade—not only in PTC but also in oxyphil cells in the context of HT [86].

Further, experimental data unravel that the RET/PTC1 exogenously expressed on normal human thyroid cells induces an inflammatory milieu involving crucial chemokines and their receptors, promoting functions vital for tumor progression, such as proliferation and survival of cancer cells [e.g., CXCR4/CXCL1] as well as neo-angiogenesis (e.g., CXL1, 2, 3, 5, 6, and 8) [87].

Additionally, a constellation of RET/PTC1-induced molecules fosters the genesis and evolution of cancer, including (i) matrix metalloproteinases (MMPs) and dipeptidyl peptidase IV (DPP IV), molecules crucial for tissue remodeling, tumor invasiveness, and neo-angiogenesis [87]; (ii) urokinase-type plasminogen activator (UPA) and urokinase-type plasminogen activator receptor (UPAR), involved in cancer progression and metastasis [87]; (iii) L-selectin [87], an adhesion molecule facilitating metastasis [88]; and (iv) osteopontin (OPN) and CD44, implicated in proliferation and invasion of transformed PCCL 3 cells, rat thyroid follicular cells [89].

An intriguing RET/PTC3-induced mechanism pivotal for tumor progression is the recruitment of CD11b+Gr1+ myeloid-derived suppressor cells, providing cancer cells with the advantage of evading immune surveillance [90, 91].

However, skepticism raise the technical limitations of the applied PCR techniques and the lack of reproducibility of the results of studies detecting the RET/PTC rearrangements in HT [92]. Furthermore, the equivocal nature of RET/PTC-induced transcriptional program—tumor-promoting versus antitumor—should be considered [87].

### **5.3 The immune attack against PTC triggers thyroid autoimmunity**

The association of PTC with HT seems more intricate than initially conceived in view of a seminal cyclic model governed by the overactive immune response, acting as a driving force for carcinogenesis, while being also a marker of tumor immunity [93]. An assumption that merits further exploration is whether the cross reaction of antitumor immunity with normal thyrocytes may precipitate HT in PTC patients genetically predisposed to thyroid autoimmunity, consolidating the hypothesis of “tumor defense-induced autoimmunity” [29]. With the advent of the era of cancer immunotherapy, new light on the coexistence of HT with PTC is shed by the increasingly reported development of HT as an adverse event of the monoclonal antibodies blocking programmed cell death (PD) protein 1 (PD-1) and PD ligand 1 (PD-L1). This revolutionary anticancer treatment unleashes the antitumor immunity at the expense of abrogating the self-tolerance, exemplifying the “tumor defense-induced” immunity [94]. For instance, a loss of circulatory PD1+ CD4+ and CD8+ T cells, an increase in peripheral CD56+CD16+ NK cells and an increase in activated monocytes have been implicated in pembrolizumab (anti-PD1 monoclonal antibody)-induced thyroiditis [94].



## 6. Does the coexistence of HT with PTC really exist?

An issue of major concern is whether the coexistence of PTC with HT is real or a myth nurtured by methodological pitfalls implicit in studies addressing this issue.

The great variety of the incidence of the coexistence of PTC with HT ranging from 0.5 to 38% [95] or, alternatively, from 5 to 85% is noticeable [96]. The results of the meta-analyses addressing the coexistence of PTC with HT are highly divergent [40, 48, 96, 97], as depicted in **Table 1**. The broad array of the mean rate of PTC among patients with HT extending from 1.1 to 40.1% blurs the landscape [97]. Nevertheless, according to a systematic review, the correlation of PTC with HT is statistically significant with a relative risk (RR) of HT among PTC equal to 2.36 and a RR of PTC among HT equal to 1.40 [98].

In an attempt to annotate the diverse epidemiological profile of the coexistence of PTC with HT, attention should be paid to the discrepancy among pertinent studies concerning the design, the enrolled populations, and the histopathologic definitions of HT [99]. Moreover, certain caveats hamper hitherto the interpretation of the lymphocytic infiltration and the positivity of thyroid autoantibodies. Firstly, thyroid lymphocytic infiltration confirmed on histology has been significantly associated with PTC even in the absence of thyroid autoantibodies [100]. Secondly, the pattern of Tg recognition by anti-thyroglobulin autoantibodies (TgAbs) differs between autoimmune and non-autoimmune thyroid disorders, being more restricted in autoimmune disorders as compared with nodular goiter and PTC harboring no thyroid lymphocytic infiltration [101]. However, in PTC correlated with histopathologically confirmed HT, the pattern of Tg recognition does not differ from that observed in HT [101]. Thirdly, it should be mentioned that the thyroid autoantibodies may be detected in healthy individuals [102]. Finally, the discordance among available TgAbs assays should be considered [103].

Another hurdle in evaluating the coexistence of PTC with HT is the selection bias inherent in data derived from surgical specimens wherein the prevalence of PTC is a priori higher than that in fine needle aspiration biopsy (FNAB) studies.

Reference	Results
Moon et al. [48]	PTC coexistent with HT is negatively associated with ETE (OR: 0.74, 95% CI, 0.68–0.81), LNM (OR: 0.82, 95% CI, 0.72–0.94), distant metastasis (OR: 0.49, 95% CI, 0.32–0.76), and recurrence (RR: 0.50, 95% CI, 0.41–0.61)
Lee et al. [96]	Frequency of HT in PTC: ≈23% 2.8 times higher occurrence rate of HT in PTC than in benign thyroid diseases ( $p < 0.001$ ) 2.4 times higher incidence of HT in PTC than in other TC ( $p < 0.001$ ) Significant association of PTC concurrent with HT with female sex (OR: 2.7; $p < 0.001$ ), multifocality (OR: 1.5, $p = 0.010$ ), absence of ETE (OR: 1.3, $p = 0.002$ ) and LNM (OR: 1.3, $p = 0.041$ ), long recurrence-free survival (HR: 0.6, $p = 0.001$ )
Lai et al. [97]	Range of mean rate of PTC among patients with HT: 1.12–40.11% Overall pooled OR of PTC risk for HT (HT versus non-HT): 2.12 (95% CI, 1.78–2.52)
Singh et al. [40]	2.77 times elevated rate of PTC in patients with HT compared with control population (OR: 2.77, 95% CI, 1.24–6.21) 1.89 times higher rate of HT in patients with PTC compared with other TC types (OR: 1.89, 95% CI, 1.02–3.50) Increased PTC-free survival in patients with coexistent HT ( $r$ : 0.08, 95% CI, 0.05–0.12) Increased overall survival in PTC patients with coexistent HT ( $r$ : 0.11; 95% CI, 0.07–0.14)

Abbreviations: CI, confidence interval; ETE, extrathyroidal extension; HR, hazard ratio; HT, Hashimoto's thyroiditis, LNM, lymph node metastasis; OR, odds ratio; PTC, papillary thyroid carcinoma, RR, risk ratio; TC, thyroid cancer.

**Table 1.**  
 Meta-analyses addressing the correlation of PTC with HT.



Jankovic et al. showed that the average prevalence rate of PTC in HT patients differed significantly between FNAB and thyroidectomy studies: 1.20 and 27.56%, respectively. Likewise, the relative risk of PTC in HT patients extended from 0.39 to 1.00 in the FNAB studies, significantly lower than that observed in the thyroidectomy studies (1.15–4.16) [37]. In that respect, Castagna et al. demonstrated absence of association of nodular HT with TC based on cytology. The same authors observed a significantly higher prevalence of DTC in nodular HT compared to nodular Graves' disease, nodular goiter with either negative or positive thyroid autoantibodies, according to surgical series. This result raised the possibility of selection bias ascribed to the fact that 60.7% of patients with nodular HT underwent surgery due to cytological data suspicious of thyroid malignancy [38]. The FNAB data from 10,508 patients revealing no statistically significant relationship between PTC and HT are consistent [104].

Nevertheless, the fear of the selection bias was abolished by the recent demonstration of a significant association of PTC with HT based on either pathological examination of surgical specimens or FNAB studies [60].

## **7. Effect of HT on coexistent PTC: host protective or tumor protective?**

Irrespective of whether HT is etiologically linked to PTC or merely judged “guilty by association,” the importance of this coexistence lies on its clinical significance. Since a complex immune network has been considered a core component of PTC microenvironment, it is rational to assume that HT—the epitome of aberrant immune reaction—influences the progression of coexistent PTC [105]. In that respect, the positive association of a favorable outcome of coexistent PTC with HT, tumor-associated macrophage infiltration, and CD8+ lymphocytes highlights the antitumor potential of the immunological landscape intrinsic in HT [106]. The recently reported negative correlation of ROR $\gamma$ t—a nuclear transcription protein of Th17—with lymph node metastases in PTC concurrent with HT is consistent. In fact, ROR $\gamma$ t is positively associated with the upregulation of caveolin 1, a tumor suppressor gene [107]. Another plausible mechanism underlying the host-protective effect of HT coexistent with PTC could be the lower frequency of BRAF V600E mutation—a genetic alteration associated with aggressive PTC phenotype—in PTC concurrent with HT compared with PTC alone [41, 42].

A rich repertoire of features indicative of auspicious PTC prognosis are significantly associated with coexistent HT, including increased relapse-free and overall survival [39], increased survival rate [96, 108], decreased risk of recurrence [108], lower rate [108] or absence of extrathyroidal extension [96], and lower rate [41] or absence of lymph node metastases [96], observed in PTC coexistent with HT compared with PTC alone. The results of a recent meta-analysis including 71 published studies with 44,034 participants revealing that PTC coexistent with HT significantly correlated with reduced incidence of extrathyroidal extension, lymph node, and distant metastasis and increased recurrence-free survival duration compared with PTC alone are seminal [47]. Noticeably, the coexistence of HT with PTC has been proven an independent indicator of favorable prognosis of PTC [105], irrespectively of the extent of lymph node dissection [46], though inconsistently [108]. On the other hand, the reported absence of host-protective effect of HT on coexistent PTC [42–45] hampers the endorsement of HT as a prognostic PTC biomarker.

In fact, the inflammatory cell infiltration of tumor microenvironment plays an equivocal role, tumor-promoting versus antitumor, posing a “Dr. Jekyll or Mr. Hyde” enigma [109]. Challenging is the illumination of the precise factors that define the fate of cancer cells in the context of the interface of PTC with HT.

## **8. Thyroid autoantibodies in the context of HT coexistent with PTC: predictive and/or prognostic PTC biomarkers or not?**

Whether HT constitutes the driving force for PTC or *vice versa* remains elusive; nevertheless, the thyroid autoantibodies, the landmark of HT, and especially the anti-thyroperoxidase autoantibodies (TPOAbs)—a more sensitive marker of HT than the TgAbs—merit interrogation as potential hallmarks of the interrelationship of PTC with HT.

A great body of evidence sustains that the positivity of thyroid autoantibodies translates into predictive and prognostic knowledge. In particular, the positivity of TPOAbs [49, 52, 53], TgAbs [51, 53, 110], as well as TPOAbs coexistent with TgAbs [52], has been shown to harbor a predictive value. Moreover, the positivity of TPOAbs [52, 57] and TgAbs [50–53, 110] has been designated as an independent predictive factor for thyroid malignancy in nodular goiter. Interestingly, the coexistence of TgAbs and TPOAbs is associated with a PTC risk greater than that connected with isolated positivity of either TgAbs or TPOAbs [52]. A host-protective role of TPOAbs in the context of coexistent PTC has been demonstrated [27, 54, 55], rationalized by the speculation that the TPOAbs exert a cytotoxic effect [110].

However, skepticism imposes a multivariate analysis failing to consolidate the host-protective effect of thyroid autoantibodies in the case of coexistent PTC [55]. Importantly, awareness raises the correlation of the positivity of thyroid autoantibodies with features indicative of ominous PTC prognosis, such as advanced disease stage [52]. As a potential link between positive thyroid autoantibodies and aggressive phenotype of PTC could be suggested the excess iodine intake that unmasks a cryptic epitope on Tg, triggering the development of TgAbs [33, 34], while exerting stimulative effect on the genesis of BRAF V600E mutation as well [111]. However, this hypothesis is debunked by the observation that the BRAF V600E mutation in DTC is inversely correlated with coexistent HT [42]. In the light of the foregoing, the designation of thyroid autoantibodies as predictive and/or prognostic biomarkers of PTC is not yet feasible.

## **9. Elevated TSH levels in HT coexistent with PTC: the mediator of the effect of HT on PTC?**

Considering that TSH constitutes a growth factor for thyrocytes [58], rational is the designation of increased, even within the normal range, serum TSH levels, in the case of PTC concurrent with HT, as a predictor of PTC risk [49, 52, 58] and a harbinger of aggressive tumor behavior [55, 59].

A strong argument in favor of the role of TSH in thyroid tumorigenesis is the detection of activating mutations of TSH receptors (TSH-R) in DTC [112]. Moreover, the cross-talk between the TSH-R/protein kinase A (PKA) signaling transduction and the well-recognized oncogenic pathways involving Wingless/int-1 (Wnt), PI3K, and MAPK has been implicated in initiation and progression of TC [113]. However, many arguments against the pathogenetic role of TSH in TC have been raised [114–117].

Nevertheless, the demonstration of HT as a risk factor for PTC in univariate analysis while being a host-protective factor in multivariate analysis after controlling TSH levels should be mentioned [61]. Similarly, multivariate analysis showed that increased TSH levels were an independent risk factor of malignancy in most FNAB studies, albeit not consistently related to HT [60]. Consequently, the subclinical or overt hypothyroidism due to autoimmune destruction of thyroid—and not HT per se—could be the real culprit for the increased PTC risk in the context of HT.

Experimental data derived from mouse models suggest the TSH-induced signaling mediated via cyclic adenosine monophosphate (cAMP) as a prerequisite for the BRAF V600E-stimulated PTC genesis, providing a plausible explanation for the implication of elevated TSH levels in PTC [62]. Furthermore, a protein kinase C (PKC)-mediated pathway has been demonstrated *in vitro* to transduce the TSH-induced signaling, dictating the invasiveness and the growth of human follicular TC cell lines [118].

However, the reported association of subclinical hypothyroidism with a less aggressive PTC phenotype compared with euthyroidism cannot be ignored [119]. Consistent is the higher risk of DTC enclosed in HT requiring low levothyroxine (LT4) replacement doses as compared with HT-induced hypothyroidism requiring higher LT4 replacement doses [27]. A hypothesis mandating further exploration is that the toxic effect of TSH mediated by  $H_2O_2$ —an element essential for thyroid hormone synthesis being simultaneously a mitogenic and mutagenic factor—concerns the residual functioning thyroid tissue, while sparing the completely destructed thyroid [27].

Intriguingly, according to the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, low TSH levels may induce DTC [63], likely forming a less differentiated epithelium susceptible to malignant transformation [27]. Interestingly, two genetic variants predisposing to PTC located on 9q22.23 and 14q13.3 have been also associated with low TSH levels [120]. Consequently, the perplexing role of TSH in PTC fuels a contention regarding the endorsement of TSH levels as predictive and/or prognostic biomarker of PTC.

## **10. Conclusions**

Despite the major strides toward the elucidation of the correlation of PTC with HT, integrating coexistent HT *per se*, as well as thyroid autoantibodies and TSH levels into PTC risk stratification systems, awaits further consolidation. Translating the coexistence of PTC with HT into the therapeutic approach of PTC is currently uncertain. A burning question is whether the broad clinical spectrum of HT, mirroring the wide array of HT histopathology, defines the trajectory of the coexistence of PTC with HT. The designation of HT as a premalignant lesion or PTC as a precipitating factor for HT is thwarted by the blurred, till now, pathogenetic landscape. Illuminating the temporal precedence, a parameter *sine qua non* for the embracement of a causal relationship between PTC and TC, is daunting. Nevertheless, harnessing the immunological link between PTC and HT should guide future efforts in clinical research, aiming to widen the horizons of immunotherapy.

In the interim, active surveillance of HT cannot be undermined, since it yields a tangible perspective of a prompt therapeutic intervention in the case of coexistent PTC.

Nonetheless, striking is, to date, the dearth of solid evidence to guide clinical decision-making on surveillance of HT based on the presumptive correlation thereof with PTC; in fact, a patient-oriented standard of care of HT should be applauded. Although thyroid ultrasonography (US) is not required for diagnosing and monitoring the majority of HT, an individualized approach should be endorsed in clinical settings. Bearing in mind the negativity of TPOAbs and/or TgAbs in 10% of HT patients [121] and approximately 20% of patients with subclinical hypothyroidism [122], identifying a hypoechoic or an inhomogeneous US thyroid pattern will provide invaluable information as regards the diagnosis of HT. Even though a thyroid/neck US is not routinely recommended unless a palpable thyroid lesion is detected [7], averting underdiagnosis of a PTC smaller than 1 centimeter (cm) in greatest dimension—the so-called papillary thyroid microcarcinoma—raises

awareness. In that respect, US could unravel a nodular variant of HT that merits further evaluation. The management of nodules in the context of HT is governed by the rules applied for any thyroid nodule irrespectively of HT, based on US-guided stratification of risk of malignancy [7]. FNAB is indicated in (i) nodules equal to or larger than 1 cm in greatest dimension presenting sonographic features of high or intermediate suspicion for PTC, (ii) nodules equal to or greater than 1.5 cm in greatest dimension presenting sonographic features of low suspicion for PTC, and (iii) nodules equal to or greater than 2 cm in greatest dimension presenting features of very low suspicion for PTC. Lower size cutoffs are embraced in the presence of clinical risk factors for PTC [7]. Pending the illumination of the clinical significance of the correlation of PTC with HT, clinicians should rely on their discretion and judgment, implementing the principle "*primum non nocere*."

### Conflict of interest

The authors declare no conflicts of interest.

### Acronyms and abbreviations

AKT	protein kinase B
B7H1	B7 Homolog 1
cAMP	cyclic adenosine monophosphate
CCL	chemokine (C-C motif) ligand
CD	cluster of differentiation
cm	centimeter
COX-2	cyclooxygenase-2
CRI	cancer-related inflammation
CXCL	CXC chemokine ligand
CXCR4	CXC chemokine receptor 4
DCs	dendritic cells
DN	double negative
DPP IV	dipeptidyl peptidase IV
DTC	differentiated thyroid cancer
ERKs	extracellular signal-regulated kinases
FasL	Fas ligand
FNAB	fine needle aspiration biopsy
HIF-1	hypoxia-inducible factor-1
HLA	human leukocyte antigen
HLA-G	histocompatibility antigen, class 1, G, known also as human leukocyte antigen G
HT	Hashimoto's thyroiditis
IL	interleukin
iNOS	inducible nitric oxide synthases
LT4	levothyroxine
M	macrophages
MAPK	mitogen-activated protein kinase
MCP-1	monocyte chemoattractant protein 1
MMPs	matrix metalloproteinases
N	neutrophils
NK	natural killer
OPN	osteopontin



PD	programmed cell death
PD-1	PD protein 1
PD-L1	programmed cell death ligand 1
PI3K	phosphoinositide 3-kinase
PKA	protein kinase A
PKC	protein kinase C
PTC	papillary thyroid carcinoma
PTEN	phosphatase and tensin homolog
RET	rearranged during transfection
RNS	reactive nitrogen species
ROS	reactive oxygen species
TC	thyroid cancer
TgAbs	anti-thyroglobulin autoantibodies
TGFb	transforming growth factor b
Th	T-helper
TLR	Toll-like receptors
TNFa	tumor necrosis factor a
TPOAbs	anti-thyroperoxidase autoantibodies
Treg	T regulatory cells
TSH	thyroid-stimulating hormone
TSH-R	TSH receptor
UPA	urokinase-type plasminogen activator
UPAR	urokinase-type plasminogen activator receptor
US	ultrasonography
VEGF	vascular endothelial growth factor
Wnt	Wingless/int-1

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