Review Article

Clinical and Pathological Implications of Concurrent Autoimmune Thyroid Disorders and Papillary Thyroid Cancer

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Cooccurrences of chronic lymphocytic thyroiditis (CLT) and thyroid cancer (DTC) have been repeatedly reported. Both CLT and DTC, mainly papillary thyroid carcinoma (PTC), share some epidemiological and molecular features. In fact, thyroid lymphocytic inflammatory reaction has been observed in association with PTC at variable frequency, although the precise relationship between the two diseases is still debated. It also remains a matter of debate whether the association with a CLT or even an autoimmune disorder could influence the prognosis of PTC. A better understanding about clinical implications of autoimmunity in concurrent thyroid cancer could raise new insights of thyroid cancer immunotherapy. In addition, elucidating the molecular mechanisms involved in autoimmune disease and concurrent cancer allowed us to identify new therapeutic strategies against thyroid cancer. The objective of this article was to review recent literature on the association of these disorders and its potential significance.

1. Introduction

Thyroid cancer is the most common endocrine malignancy and was considered responsible for 1600 deaths amongst 300,000 patients diagnosed with the disease in the USA in 2009 [1]. The incidence of differentiated thyroid cancer (DTC) in the United States and worldwide continues to increase, having more than doubled over the past three decades [2, 3]. A similar trend has been observed in other countries across Europe, Asia, Oceania, and South America [4]. In fact, only a few countries have reported a decline in thyroid cancer incidence: Sweden (18% reduction for both men and women), Norway (5.8% reduction for women), and Spain (25.9% reduction for women) [4]. The disease incidence is increasing in other European countries, such as Switzerland (5.3%) and France (155.6%) [4]. A common aspect in all epidemiological reports is that the highest rate of increase is for small and localized thyroid cancers, which probably contributes to the stable and relatively low mortality observed. However, there are several lines of evidence indicating that the increased incidence of DTC is also related to other factors, including the increasing amount of large tumors that would certainly be detected without the need for more sophisticated or sensitive imaging methods and a parallel increase of exposure to a series of environmental factors associated with cancer, such as exposure to radiation [5, 6]; living in volcanic areas [7]; iodine intake [8, 9]; female gender [10], which might be related to estrogen, a subject that is being studied for our group; obesity [11]; and genetic factors that might be related to susceptibility to DTC [12–17].

A parallel increase has been observed in the incidence of autoimmune thyroid diseases, such as thyroiditis. Chronic lymphocytic thyroiditis (CLT) and DTC, mainly PTC, share some epidemiological features, such as the relationship with ionizing radiation exposure [6, 18] and dietary iodine [19, 20]; both also share some molecular features [21–28] and are more likely to occur in women than in men [29–31].

Although most tumors originate from follicular cells, they present remarkably different features. In addition, likewise breast, prostate, and other human neoplasias, microscopic thyroid tumors are frequently found at autopsies and in surgical specimens [32]. However, the impact of the immune system, the presence of autoimmune thyroid diseases, and their relationship with cancer development is a matter of controversy [4]. Also, literature repeatedly reports association between CLT and thyroid cancer. Geographically widespread association and incidence of CLT with thyroid cancers are shown on Table 1.

2. Concurrent Chronic Lymphocytic Thyroiditis (CLT), Thyroid Autoimmune Diseases, and Differentiated Thyroid Carcinomas (DTC)

Hashimoto's disease and Graves' disease are the two most common forms of autoimmune thyroiditis (AT), the archetypal organ-specific autoimmune disease in humans. Both are characterized by lymphocytic infiltrate and autoreactivity against thyroid autoantigens [43–45].

Chronic lymphocytic thyroiditis (CLT) is an autoimmune disease characterized by widespread lymphocyte infiltration, fibrosis, and parenchymal atrophy of thyroid tissue. Hashimoto's thyroiditis (HT) is characterized by infiltration of the thyroid gland by inflammatory cells, often followed by hypothyroidism due to destruction and eventual fibrous replacement of the parenchymal tissue. In HT, the body also produces autoantibodies to thyroid-specific antigens (Figure 1), considering that thyroglobulin (Tg) and thyroperoxidase (TPO) are the two primary antigens in AT [46–48]. HT is characterized by a gradual loss of thyroid function, goiter, and T-cell infiltration in histology, affecting women more often than men, with a sex ratio of 7 : 1, and occurring in genetically susceptible populations, but lacking a strong association with HLA. The overriding feature of HT is the progressive depletion of thyroid epithelial cells, which are gradually replaced by mononuclear cell infiltration and fibrosis [47, 49, 50]. In thyroiditis, especially HT, parenchyma of thyroid gland is progressively lost and replaced by cells of the inflammatory infiltrate that produce chemokines, cytokines, and growth factors, most of which are under NF-β transcriptional control. The persistent stimulation of residual thyrocytes with such molecules could induce the activation of NF-β in follicular cells, thereby creating a functional network between thyroid epithelial cells and inflammatory cells [49].

In a number of human malignancies, the presence of lymphocytic infiltration in or around a tumor is commonly viewed as representing a host immune response [52]. Although the presence of tumor-associated lymphocytic infiltration is widely regarded as representing a host immune response, the impact of this inflammatory response on tumor behavior may be variable [28, 53–55]. In addition to the common occurrence of CLT and papillary thyroid carcinomas (PTC), it has been suggested that the relatively high prevalence of apparently indolent PTC in an autopsy series may represent host immune control [56].

The relationship between CLT and PTC was first proposed by Dailey et al. in 1955 [21]. Since this initial description, the association between the diseases has been repeatedly reported and highly debated in the literature, remaining controversial.

A thyroid lymphocytic inflammatory reaction has been observed in association with PTC at variable frequency, ranging from 0.5% to 58% [21–28, 34, 37, 39, 40, 57, 58]. This wide distribution of coexisting CLT and PTC reported in a number of studies may be due, at least in part, to differences in the level of histological examination and criteria of autoimmunity characterization, patient selection or indications for thyroidectomy, environmental factors (history of radiation exposure) [59], genetic or population background [57], and geographic factors (e.g., the amount of iodine intake) [59–61].

Thyroid autoimmunity is a broad spectrum disease also manifested as the presence of antithyroid antibody (ATA). A series of reports indicate a close association between ATA and malignancy [50, 62], while others are not able to confirm this association [63–66]. Boi et al. assessed ultrasound- (US-) guided fine-needle aspiration cytology obtained from 590 unselected consecutive patients with single thyroid nodules and positive or negative serum antithyroid antibody. Cytological results were divided into three classes of increased risk of malignancy: low risk or benign, indeterminate risk, and suspect or malignant. They suggested that the presence of antithyroid antibodies confers an increased risk of suspicious or malignant cytology in unselected thyroid nodules [62]; even this result is not confirmed in other reports [67, 68].

There are reports in the literature on the relationship between other thyroid autoimmune diseases, such as Graves's disease and thyroid cancer. Some studies have suggested a high incidence of malignant thyroid nodules in patients with Graves' disease and hyperthyroidism, and that thyroid cancer behaves more aggressively when associated with Graves' disease, although still controversial [69–72]. As TSH stimulates growth of metastatic differentiated thyroid cancer expressing the TSH receptor (TSHR), it is possible to hypothesize that high levels of anti-TSHR antibodies of Graves' patients might stimulate thyroid cancer growth and early metastatic spread, thus negatively affecting patient outcome, as reviewed by Belfiore et al. [73]. However, other studies do not support the suggestions that thyroid cancer in patients with Graves' disease is more aggressive than in either patients with toxic nodular goiter or euthyroid subjects, suggesting that concurrent Graves disease is not a good prognosticator [74, 75].

Even in reduced frequency, CLT is also presented in association with follicular thyroid carcinoma (FTC). Loh et al. [37] studied subjects with lymphocytic thyroiditis (LT), including Hashimoto's thyroiditis and cell lymphocytic infiltrates around thyroid neoplasms. Lymphocytic thyroiditis (LT) was recorded in 125 of 564 patients (22%) with PTC histology, when comparing with three of 67 patients (4.5%) with follicular or Hürthle cell histology. They found that patients with LT almost uniformly had PTC, consistent with the observation by other investigators [33, 34, 76, 77]. In fact, Souza et al. [38] reported that TPO

Table 1: Last twenty years of published results. Autoimmune manifestation was significantly correlated with the presence of follow-up features, disease presentation features, and individual features.

Reference	Autoimmune manifestation	Type of thyroid cancer	Number of patients	Follow-up features	Disease presentation features	Individual features	Geographic widespread	Concurrent CIT in thyroid cancer (%)
[33]	Lymphocytic infiltration	PTC	95	Relapse-free	Circulating autoantibodies, coexisting thyroid disease	None	Japan	37.89
[34]	Chronic lymphocytic thyroiditis	PTC	1533	Relapse-free, overall survival	None	None	Japan	18.09
[35]	Chronic lymphocytic thyroiditis	PTC	69	None	Multifocality	None	Japan	21.74
[36]	Lymphocytic infiltration	PTC+FTC+MTC+ATC	153	None	Low pT stage	None	Germany	17.65
[37]	Both Hashimoto's thyroiditis and lymphocytic infiltration	PTC+FTC	631	Low cancer recurrence rate, low cancer mortality rate	Low extrathyroidal invasion, nodal metastases, distant metastases, pTNM stage	Female	USA	20.28
[28]	Hashimoto's thyroiditis and lymphocytic infiltration separately	PTC	136	Overall survival	Multifocality, Tumor Infiltrating lymphocytes	Young, female	USA	30.15
[38]	Circulating autoantibodies and history of autoimmune thyroid disease	PTC+FTC	173	Relapse-free, overall survival	None	None	Brazil	8.67% (+TPOAb) + 6.94% (+TgAb) + 13.87% (with Graves or Hashimoto history)
[39]	Hashimoto's thyroiditis	PTC	101	None	None	Old	Korea	36.6
[40]	Chronic lymphocytic thyroiditis	PTC	1441	Relapse-free	Small tumors, low pTNM stage	Female	Korea	14.85
[41]	Lymphocytic infiltration and/or circulating autoantibodies	PTC	343	None	None	None	Italy	37.31
[42]	Chronic lymphocytic thyroiditis	PTMC	323	None	TgAb positive, Microsomal Ab positive, multifocality, and bilaterality	Female	Korea	32.51

PTC: papillary thyroid carcinoma; FTC: follicular thyroid carcinoma; PTMC: papillary thyroid microcarcinoma; MTC: medullary thyroid carcinoma; ATC: anaplastic thyroid carcinoma; Ab: antibody.
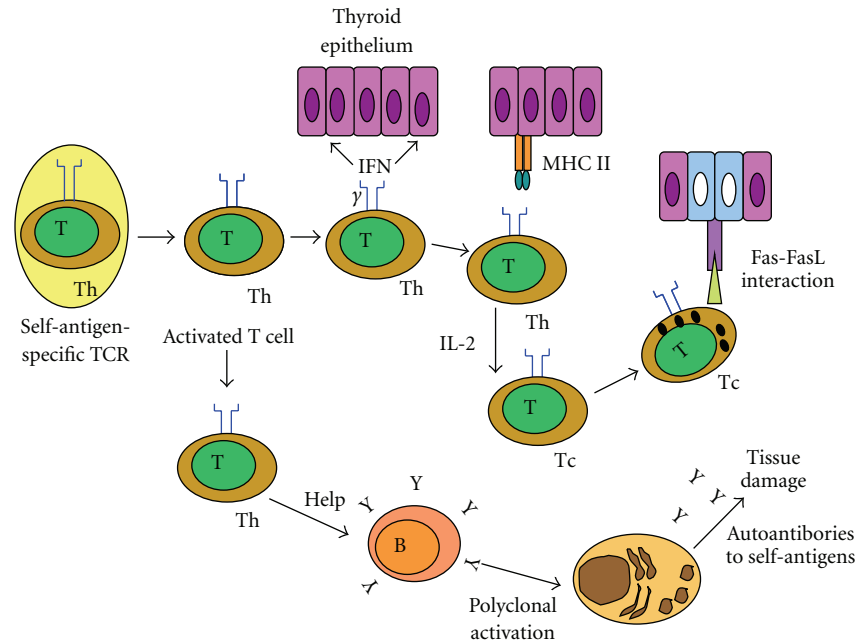
Figure 1: Activation of a self-specific T-cell initiates a cascade of events that amplifies the immune response and involves both CD4 and CD8 T cells, inducing an antibody-mediated response. B: B cells; IFN-γ: interferon-γ; IL-2: interleukin-2; MHCII: major histocompatibility class II; T: T cells; Tc: cytotoxic T-cell; Th: T helper cell (adapted from [51]).

antibody was present in 14 of 123 patients (11.3%) with PTC histology, when comparing with one of 50 patients (2%) with follicular or Hürthle cell histology. In addition, thyroglobulin antibody (TgAb) was present in 12 of 123 patients (9.76%) with PTC, while none of FTC patients presented TgAb at diagnosis, confirming the correlation between concurrent autoimmunity and PTC histology.

3. Molecular Link between Thyroid Cancer and Chronic Lymphocytic Thyroiditis

A functional relationship between chronic inflammation and cancer was first proposed by Virchow, in 1863, and has been sustained by clinical [41, 78] and epidemiological evidence [79–82]. Both a causal association and a noncausal association have been proposed, and the molecular mechanism that links inflammation and cancer is not completely clear so far. A link between thyroid cancer, in particular the PTC histotype, and AT has long been recognized, although the precise relationship between the two diseases remains subject of debate.

Hashimoto's thyroiditis is characterized by proliferating nodules as well as by cytological alterations and nuclear modifications similar to those of papillary carcinomas, suggesting that both neoplastic and autoimmune diseases could share the same molecular pathogenesis [83].

The mitogen-activated protein kinase (MAPK) signaling pathway is a foremost event in the carcinogenesis of the most common endocrine malignancy, the papillary thyroid carcinoma (PTC). Affected elements include RET/PTC rearrangements and point mutations of the *RAS* and *BRAF*

genes. Mutations in these genes are found in over 70% of PTC, as previously reviewed [84]. Chromosomal RET rearrangements, called RET/PTC, result in constitutive ligand-independent activation of RET kinase, which was the first genetic anomaly detected in PTC and is found in 5–70% of tumor samples. Although less frequently, the activation of other tyrosine kinase receptors, including NTRK1, c-Met, or EGFR, has also been reported in PTC [85]. The *BRAF* mutation represents the most common genetic alteration found in PTC [86]. More than 90% of *BRAF* mutations lead to a change of valine to glutamic acid at position 600 (V600E) [85]. Finally, RAS is the least affected molecule in the pathway [85]. All of these multisteps of thyroid carcinogenesis are shown in Figure 2.

Several authors have found RET/PTC rearrangements in non-neoplastic thyroid lesions, such as CLT [88–90]. In addition, Muzza et al. found RET/PTC1 being more represented in PTCs associated with autoimmunity than in PTC without autoimmunity, suggesting that the association between RET/PTC1 and thyroiditis points to a critical role of this oncoprotein in the modulation of the autoimmune response [41]. Rhoden et al. showed that low-level RET/PTC recombination occurs in nonneoplastic follicular cells of HT and in a subset of papillary thyroid carcinomas, indicating that overlapping molecular mechanisms may govern early stages of tumor development and inflammation in the thyroid [91]. Kang et al. studied the RET/PTC-RAS-BRAF in oxyphil cells in the vicinity of large lymphoid HT infiltrates and in malignant PTC cells. The expression of RET, nuclear RAS, and ERK proteins is greatly enhanced in PTC cells and HT oxyphil cells. Thus, the RET/PTC-RAS-BRAF cascade may be involved in the development of PTC and oxyphil
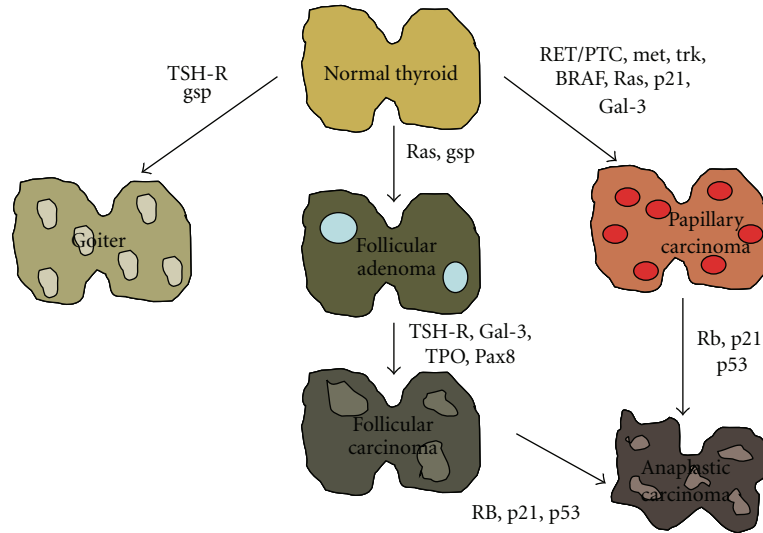
FIGURE 2: Multistep carcinogenesis model of thyroid cancer formation. Formation of benign thyroid tumors occurs as a result of alteration of various growth factors. Follicular neoplasms are formed from thyrocytes by mutations of RAS and other factors, as shown in the figure. Papillary cancers are formed by alterations in RET/PTC and other oncogenes. Undifferentiated tumors are formed from differentiated tumors by mutations of tumor suppressor genes (adapted from [87]).

cell metaplasia in HT. These results show the possibility of a molecular link between oxyphil cell metaplasia in HT and the progression of PTC [92].

However, different mechanisms could also explain the association between CLT and RET/PTC rearrangement (Figure 3). Chronic inflammation might facilitate the rearrangement or, conversely, RET/PTC rearrangement might promote chronic inflammation. The production of free radicals, cytokine secretion, cellular proliferation, and other phenomena correlated with inflammation might predispose to the rearrangement in follicular cells [93]. It is well known that leukocytes recruited under an inflammation context physiologically secrete reactive oxygen species and reactive nitrogen species. However, these highly reactive metabolites induce the production of peroxynitrite and other mutagenic agents, leading to "DNA damage", for example, mutations in proliferating cells [94]. Thus, in the case of persistent tissue damage, O_2 and N highly reactive metabolites secreted by inflammatory cells induce point-mutations, DNA rearrangements, and double-strand breaks [93, 95].

Guarino et al. proposed that cytokines and chemokines released by inflammatory tumor stroma could sustain the survival of thyroid cells in which RET/PTC rearrangements randomly occur, thereby allowing the selection of clones that acquire additional genetic lesions and thus become resistant to oncogene-induced apoptosis [93]. In fact, some reports indicate that RET/PTC might induce apoptosis [96, 97]. This hypothesis of interaction between RET/PTC rearrangement and thyroid inflammation is reinforced by some studies that suggest that thyroid cancer cells, like other epithelial cancer cells, can produce inflammatory factors that may facilitate cell survival, preventing apoptosis. Stassi et al. found that autocrine production of IL-4 and IL-10 promotes thyroid tumor cell progression and resistance to

chemotherapy by the upregulation of antiapoptotic proteins, such as Bcl-2 and Bcl-xL [98]. Conticello et al. found that IL-4 protects tumor cells (primary prostate, breast, and bladder cancer) from CD95- and chemotherapy-induced apoptosis by the upregulation of antiapoptotic proteins, such as cFLIP/FLAME-1 and Bcl-x(L) [99]. Todaro et al. identified that primary epithelial cancer cells from colon, breast, and lung carcinomas produced interleukin-4 (IL-4), which amplified the expression levels of these antiapoptotic proteins and prevented cell death induced upon exposure to drug agents via downregulation of the antiapoptotic factors PED, cFLIP, Bcl-xL, and Bcl-2, providing evidence that exogenous IL-4 was able to upregulate the expression levels of these antiapoptotic proteins and potently stabilized the growth of normal epithelial cells making them apoptosis resistant [100].

On the contrary, RET/PTC rearrangement might induce chronic inflammation. Russell et al. found that RET/PTC3 alone increases nuclear NF-kappaB activity and secretion of MCP-1 and GM-CSF. Finally, transfer of RP3-expressing thyrocytes into mice in vivo attracted dense macrophage infiltrates, leading to rapid thyroid cell death [101]. In addition, the same group found that IL1-alpha, IL1-beta, IL6, TNF-alpha, and the Cox2 enzyme are produced by RET/PTC3-transgenic thyroid tissue, but absent from nontransgenic thyroids, providing support for the notion that oncogene-induced cytokine secretion is important for the development and progression of thyroid carcinomas in genetically permissive hosts [102]. Prostaglandin E2, microsomal prostaglandin E2, cyclooxygenase 2 (Cox2), IL24, and other genes coding for proteins involved in the immune response and in intracellular signal transduction pathways activated by cytokines and chemokines have been suggested to be induced by RET/PTC, indicating that the expression
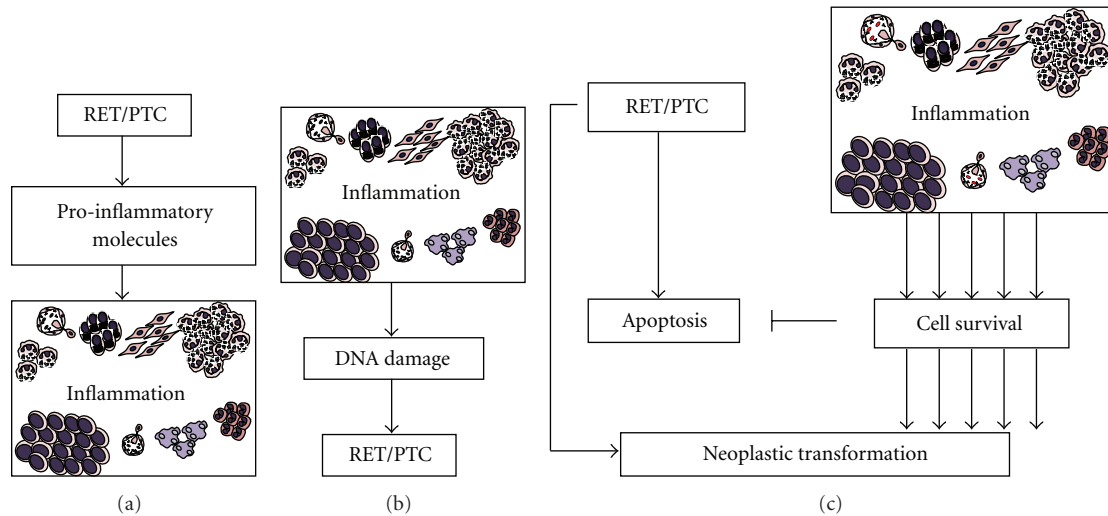
Figure 3: Putative links between RET/PTC rearrangement and concurrent thyroid inflammation. (a) RET/PTC could drive expression of several proinflammatory molecules that may elicit concurrent inflammation. Another possibility (b) is inflammation propitiating RET/PTC rearrangement. Inflammation produces reactive oxygen species and free radicals that may facilitate DNA damage and chromosomal abnormities, like RET/PTC rearrangement. (c) Molecules released by inflammation could sustain the survival of thyroid cells in which RET/PTC rearrangements randomly occur, thereby allowing the selection of clones that acquire additional genetic lesions and thus become resistant to oncogene-induced apoptosis.

of the oncogenic fusion protein RET/PTC is critical not only to thyroid cancer pathogenesis but also in the elicitation of inflammatory response [103–105].

$BRAF^{V600E}$ mutation is another common genetic alteration in PTC. Muzza et al. found $BRAF^{V600E}$ being more represented in PTC without concurrent autoimmunity [41]. Furthermore, Kim et al. found that, in Korean patients with PTC, $BRAF^{V600E}$ mutation is associated with a lower frequency of background HT [39]. Studies on melanoma cells have given clues about mechanisms linking $BRAF$ mutation and immune response. Molecules like interleukin (IL)-10, VEGF, IL-6, and IL-8 are thought to be induced by $BRAF^{V600E}$ mutation [106, 107].

The association between solid cell nest (SCN) of the thyroid and both neoplastic and autoimmune thyroid diseases is the most recent and debated issue. It is currently accepted that solid cell nests and the so-called mixed follicles are branchial body remnants [108–116], whose biological significance remains disputable [108, 109, 117–119]. Previous studies have described the histological and immunohistochemical features of SCN [108, 109, 114, 117, 120–124]. Cameselle-Teijeiro et al. suggested that main cells of solid cell nests (SCNs) might be multipotential cells that could contribute to histogenesis of C cells and follicular cells, as well as to some thyroid tumors [119]. Recently, Preto et al. and Reis-Filho et al. reported that such main cells harbor the minimal properties of a stem cell phenotype (capacity for both self-renewal, conferred by telomerase activity, and differentiation to one or more types of specialized cells, given by the high expression of p63 and bcl-2) and may thus represent a pool of stem cells of the adult thyroid [123, 125]. Burstein et al. hypothesized that SCN p63-positive cells are pluripotent and may stay

undifferentiated or undergo benign squamoid or glandular maturation, thyroid follicular epithelial differentiation, and oncogenic change leading to papillary carcinoma or may trigger an immune reaction, resulting in lymphoid infiltration and Hashimoto's thyroiditis. Hence, Hashimoto's thyroiditis and papillary carcinoma would be etiologically linked because both disorders might be initiated by the same population of pluripotent p63-positive embryonal stem cell remnants [122]. SCN could represent incompletely developed thyroid tissue predisposed to autoimmune thyroid diseases, such as Hashimoto's thyroiditis, since the epithelia from the third and the fourth pouches have the ability to attract lymphocytes [126, 127]. Cameselle-Teijeiro et al. described an unusual case of SCN hyperplasia coexisting with two papillary microcarcinomas, a follicular adenoma, hyperplastic nodules, and a few lymphoid aggregates [128]. A morphologic continuity between SCN and one papillary thyroid microcarcinoma was reported and the authors found the same $BRAF^{V600E}$ mutation in both the SCN and the contiguous papillary thyroid microcarcinoma, suggesting a histogenetic link between the main cells of SCN and PTC, raising the possibility that SCN hyperplasia could be a precursor lesion of PTC [128]. These findings suggest that SCN may be a key point in the pathogenesis of both CLT and PTC.

Pathways of immune activation could exert a role in thyroid cancer and CLT link. Toll-like receptor (TLR) comprises a family of cell surface receptors involved in the recognition of pathogen-associated signature molecules that signal the activation of innate and adaptive immunity [129–133]. Although the TLR family consists of more than ten members [133], in humans, TLR3 had been reported to be restricted primarily to dendritic cells of the immune system

[134]. Harii et al. showed that TLR3 can be functionally overexpressed in cultured human thyrocytes by stimuli. Immunohistochemical showed that TLR3 protein is overexpressed in human thyrocytes surrounded by immune cells in 100% of patients diagnosed with Hashimoto's thyroiditis, but not in normal or Graves' thyrocytes, suggesting that TLR3 overexpression can induce an innate immune response in thyrocytes, which may be important in the pathogenesis of Hashimoto's thyroiditis and in immune cell infiltrates [129]. McCall et al. showed that PTC cells basally express TLR3 RNA and that TLR3 signal systems are functional in these cells. High basal TLR3 levels and TLR3 signals capable of increasing cytokines and chemokines in PTC cells in vitro are consistent with the existence of immune cell infiltrates in vivo, based on related studies suggesting that elevated TLR3/TLR3 signals in HT are associated with immune cell infiltrates [129, 135].

Studies on DNA damage and repair have recently yielded several intriguing connections between tumor biology and immune response. There is some evidence that ATM may exert a special role in the activation of the immune response. ATM is an essential component of cell cycle restriction point control. Its scope of interaction includes phosphorylation and activation of E2F1, p53, and Cdc25 family members, which inhibit cell cycle progression and activate DNA repair systems [136, 137]. Gomez et al. showed that ATM protein expression was significantly downregulated in immunoresistant human glioma cell clones [138], indicating a possible immunogenic role of ATM gene. DNA damage signaling can directly engage the immune system in a non-cell-type-specific manner. ATM activation by genotoxic agents or stalled DNA replication induces ligands of the NKG2D receptor. These are expressed by natural killer cells and activated CD8+ T cells of the innate immune system [139]. In addition, authors indicated that polymorphisms of DNA damage response genes, such as *ATM*, *XRCC1*, *TP53*, *XRCC3*, and *MTF1*, may be potential risk modifiers of ionizing radiation-induced or sporadic PTCs [140, 141]. Royer et al. reported that hOGG1, encoding human 8-oxoguanine DNA glycosylase (hOGG1), a key enzyme for repairing DNA damaged by reactive oxygen species and loss of heterozygosity, is strongly associated with PTC and HT but not with benign thyroid, suggesting that thyroid follicular epithelia accumulate aberrant genetic changes in long-standing HT, which may represent a precursor lesion of PTC [142]. In fact, data from our group showed a significant correlation between ATM expression and concurrent CLT in DTC (not published data).

4. Prognostic Implication of the Association between CLT and PTC

It remains a matter of debate whether the association with a CLT or even an autoimmune disorder could affect the prognosis of PTC. In fact, a worse prognosis was reported in a few series [72, 143], whereas most of the studies showed either a protective effect of thyroid autoimmunity [34, 37, 40, 144] or a similar behavior between cancer with and without associated thyroiditis [41, 74], as shown in Table 1.

Our group reported a worse outcome in DTC patients with no evidence of autoimmune activity when compared with patients who reported an autoimmune thyroid disease and/or presented positive circulating thyroid autoantibodies, suggesting that autoimmune activity against the gland may exert a protective effect on the outcome of differentiated thyroid carcinoma patients [38].

However, it is unclear whether coexistent CLT represents a host immune response to DTC [33, 60, 145] or just a chance occurrence [40, 146, 147]. The favorable clinical outcome in PTC patients with concurrent autoimmunity strongly suggests that a thyroid autoimmune response may enhance or even provide an antitumor attack. CLT is an autoimmune reaction to thyroid specific antigen, and this immune response may lead to destruction of thyroid tissue. Kim et al. [40] postulated that, as PTC cells originating from follicular cells expressed specific antigen of normal follicular cells, although in a less degree, coexistent CLT might be involved in destruction of tumor cells in much the same way as in advanced CLT. This immune reaction against tumor might be associated with a better prognosis for PTC patients with CLT. Studying the glands of autopsies performed in individuals from two different Brazilian regions (Rio Grande do Norte versus São Paulo), we found a high incidence of nonencapsulated nonsclerosing papillary thyroid microcarcinomas (PTM) in Rio Grande do Norte, an area of markedly high incidence of PTC, in sharp contrast with the prevalence of small sclerosing lesions in São Paulo, where clinical thyroid cancers are much more infrequent [148]. PTMs could elicit an inflammatory lymphocytic response, fibrosis, and the formation of a capsule impeding its further growth [148]. We could speculate that these lesions may never evolve to clinical cancers, in contrast with the nonencapsulated nonsclerosing lesions that could represent early stages of clinical PTC.

Conversely, antithyroid antibodies may be able to recognize these malignant cells and destroy them in the same way as they destroy normal follicular cells, contributing to the low rate of clinical progression of these lesions [32, 62, 149].

Muzza et al. [41] found no significant differences regarding either clinical and pathological features or outcomes between two matched groups of PTC patients with and without associated autoimmunity. The cases of PTC associated with lymphocytic thyroiditis (LT) are much more often multicentric than the nonassociated form of PTC [35]. Interestingly, those with multifocal tumors had a relatively high incidence of lymphocytic thyroiditis (62%) in the remaining thyroid parenchyma during the definitive histological examination [150, 151]. Kim et al. [42] found that in metastatic papillary thyroid microcarcinomas, multifocality and bilaterality were more frequent in PTC with LT than without LT. Kim et al. [39] found that a background of Hashimoto's thyroiditis is more frequent in young patients, who trend to be patients with good prognosis. However, they found that the $BRAF^{V600E}$ mutation in PTC is associated with a low frequency of background Hashimoto's thyroiditis and high frequency of lymph-node metastasis, suggesting a paradoxical role of concurrent autoimmunity of PTC outcome.

Some investigators have reported that the presence of CLT in PTC is associated with better prognosis, low recurrence rate, and less aggressive disease at presentation [33, 34, 36, 37, 40, 152, 153]. Despite some controversies, there is an emerging literature on the protective effect of CLT in patients with PTC. In a large retrospective study, Kashima et al. reported a 5% cancer-specific mortality and a 85% relapse-free 10-year survival rate in patients without CLT compared with 0–7% mortality and 95% relapse-free 10-year survival rate with CLT [34]; this finding was very similar to Loh's results [37]. It is, however, not clear whether treatment modality, including extent of surgery, was comparable between those with and without CLT. Kebebew et al. reported that the presence of CLT was associated with an improved prognosis by univariate analysis, but it was not an independent factor [28], and this result was due to the fact that most patients with CLT had other good prognostic factors, such as young age and female gender. Kim et al. found a greater female preponderance in the patients with CLT when comparing with those without CLT. Mean tumor size in the patients with CLT was smaller than that in patients without CLT. One hundred and fifty-one (12.3%) patients without CLT had recurrence, whereas 14 (7.1%) patients with CLT had recurrence during the follow-up period [40]. Singh et al. [30] reported that the prognostic variables at the time of a diagnosis of papillary cancer and the approach to management are not altered by the presence of coexistent Hashimoto's thyroiditis. In addition, the rate of surgical complications was not higher in patients with coexistent Hashimoto's disease, suggesting that the presence of coexistent Hashimoto's thyroiditis does not affect the diagnostic evaluation or management of papillary thyroid cancers. However, meta-analysis suggested a positive correlation between Hashimoto's disease and disease-free survival and overall survival [30].

5. Future Perspectives and Conclusion

Cooccurrences of CLT and thyroid gland cancer have been repeatedly reported [21–28]. A better understanding about clinical implications of concurrent autoimmunity to thyroid cancer could lead to new insights of thyroid cancer immunotherapy. In addition, elucidation of the molecular mechanisms involved in autoimmune disease and concurrent cancer could help identify new therapeutic strategies against thyroid cancer. In fact, within the last decade, a multitude of different studies and clinical trials have been performed using immune cell therapies for different cancers. Cancer immunotherapy using dendritic cells (DC) or adoptive cytotoxic T-lymphocytes (CTLs) is very promising because malignant cells can be affected by the immune system without damaging healthy tissue and without dangerous side effects. In any case, the identification of tumor cell-specific antigens is crucial for establishing clinically effective tumor immunotherapy and monitoring the induced immune response. Up to now, however, no single tumor-associated antigen has been proven useful for primary follicular thyroid carcinomas, although a couple of candidates might have this potential [154]. Only antibody-based

therapies were performed on nonmedullary thyroid cancer, and there is a broad spectrum to be explored on cellular therapy against DTC, mainly for those cases with aggressive manifestation [155–157].

Medullary thyroid cancer (MTC) can give us an example for immunotherapy against thyroid cancer. The polypeptide hormone calcitonin has been proposed as tumor antigen for immunotherapy in MTC. Since then, several vaccination trials have been performed in murine models and also in men. In humans, several studies used full-length calcitonin for priming DCs [158, 159]. Thereafter, a new protocol with interferon-α generated DCs with direct tumor lysis activity was performed [160]. After a long-term follow-up of more than 48 months, two of five MTC patients showed stable disease with changes in tumor size and tumor marker of less than 25% [161]. More studies are warranted to apply all these concepts to poorly differentiated and anaplastic thyroid cancer.

Conflict of Interest

There is no financial interest in or arrangement with a company whose product was used in a study. In addition, there is no financial interest in or arrangement with a competing company, and there are no other direct or indirect financial connections or other situations that might raise the question of bias in the work reported or the conclusions, implications, or opinions stated—including pertinent commercial or other sources of funding for the individual author(s) or for the associated department(s) or organization(s), personal relationships, or direct academic competition.

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