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Borderline and Precursor Lesions of Thyroid Neoplasms: A Missing Link

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Abstract

There are several thyroid lesions that have been reported to be precursor, precancerous, or premalignant forms of, or predisposing factors for thyroid carcinoma. These lesions include normal thyroid with radiation history and chronic inflammation such as autoimmune thyroiditis, solid cell nest, hyperplastic adenomatous nodule, dyshormonogenetic goiter, follicular adenoma, atypical adenoma, borderline malignancy (follicular tumor of uncertain malignant potential and well-differentiated tumor of uncertain malignant potential), and some extremely low-grade thyroid neoplasms currently labeled as cancer including papillary microcarcinoma, capsular invasion only follicular carcinoma, and encapsulated papillary carcinoma. This article briefly reviews these lesions as possible precursor lesions of thyroid carcinomas, an important initial step of carcinogenesis or an early phase of progression in the multistep carcinogenesis theory.

Keywords: Thyroid gland, follicular cell, borderline malignancy, precancerous lesion, precursor lesion, carcinogenesis

I. Precursor Lesions of Thyroid Carcinoma: A Missing Link

A number of sequential events and multiple steps of thyroid carcinogenesis and corresponding genetic and epigenetic alterations, from normal follicular cells, benign proliferative lesions, benign follicular adenoma (FA), well-differentiated carcinoma (WDC), to poorly differentiated carcinoma (PDC) and undifferentiated carcinoma (UC) of thyroid, have not yet been fully elucidated (1-11). One of the major problems in adapting thyroid neoplasms into the multistep carcinogenesis model is the lack of known precursor lesions, a missing link of thyroid carcinogenesis in the multistep carcinogenesis theory (12). FA is described as a possible candidate for precursor lesions of thyroid carcinomas in many reviews and textbooks because of their morphological similarity and their common genetic alterations (*RAS* mutations and *RET/PTC* and *PAX8/PPARγ* rearrangements) (2-5, 8-11, 13-15). However, FA is not regarded as a high-risk precancerous lesion of follicular thyroid carcinoma (FTC) or papillary thyroid carcinoma (PTC), and prophylactic surgery for benign FA is not currently recommended due to infrequent progression from FA to malignant neoplasms (16-19). Furthermore, in the WHO blue book it is explained that no definite precursor lesions are known for FTC, followed by a comment that FTC may arise from FA (20). Concerning PTC, it also stated that there is no known precursor lesion for it (20). As such, no definite precursor lesions for thyroid follicular cell carcinomas are currently known, while C-cell hyperplasia or C-cell carcinoma *in situ* is accepted as a precursor lesion for C-cell (medullary) carcinoma of the thyroid (21-24). This review analyzes the literature, highlights the possible precursor lesions for thyroid carcinoma in addition to FA, and clarifies the initiation and early progression phases in the multistep carcinogenesis of thyroid follicular cell neoplasms.

II. Genetic Alteration in Morphologically Normal Looking Thyroid

Radiation is one of the risk factors of thyroid cancer, the evidence for which has been obtained from a sad history of medicine on childhood irradiation for benign diseases, nuclear accidents in nuclear power plants and the use of atomic bombs. Abend et al. evaluated gene expression profiles in 63 paired RNA specimens from normal and tumor tissues of patients who experienced the Chernobyl nuclear power plant accident during childhood (25). They concluded that the multistep process of radiation carcinogenesis begins in histologically normal thyroid tissue and may involve dose-dependent gene expression changes (25).

III. Chronic Inflammation and Autoimmune Hashimoto's Thyroiditis Predispose to Papillary Carcinoma

Chronic inflammation is regarded as a possible preneoplastic condition in several organs including the thyroid gland, and Hashimoto's chronic thyroiditis has been reported to be a high-risk condition for PTC and malignant lymphoma (26-36). Di Pasquale et al. analyzed PTC with Hashimoto's thyroiditis and found that, of the four atypical solid microscopic nodules composed of cells with clear nuclei and occasional grooves without nuclear pseudoinclusions, two were associated with PTC and the other two not. They demonstrated cytoplasmic reactivity for cytokeratin 19 and RET/PTC antibody in two of the three cases examined, and concluded that these atypical nodules may represent a precursor lesion of PTC in patients with Hashimoto's thyroiditis (29). Chiu et al. analyzed a large number of cases with thyroiditis; the follicular epithelial dysplasia was positively stained for TTF1 and thyroglobulin, and some of them also expressed p63 (26%),

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HBME-1 (86%), CK19 (96%), galectin-3 (40%) and cyclin D1 (76%) (34). They concluded that atypical microscopic lesions in chronic thyroiditis with an immunohistochemical profile similar to PTC are premalignant lesions preceding PTC (34).

Multifocal fibrosing thyroiditis (MFT) has been proposed as a risk factor for PTC, however Frank et al. analyzed *BRAF* mutations in seven cases of PTC with MFT but found none. They concluded that there is no evidence suggesting that MFT lesion is a direct precursor to PTC (37).

IV. Solid Cell Nest as Possible Stem Cells in the Thyroid Gland

Cameselle-Teijero et al. examined a case of solid cell nest hyperplasia associated with multiple PTC in a 48-year-old man with goiter. They found the same *BRAF(V600E)* mutation in both solid cell nests and adjacent papillary microcarcinoma. They concluded that solid cell nest hyperplasia is a precursor lesion of PTC (38). Reis-Filho et al. reported immunohistochemical demonstration of p63 in solid cell nest and suggested its stem cell nature (39). Furthermore, mucoepidermoid carcinoma of the thyroid and intrathyroid epithelial thymoma/carcinoma showing thymus like differentiation (ITET/CASTLE) have been postulated to originate from solid cell nests (40-42).

V. Benign Neoplastic and Non-Neoplastic Nodular Lesions

Benign proliferation of follicular cells in the thyroid gland can give rise to a variety of lesions, such as non-neoplastic proliferative lesions, benign hyperplastic adenomatous nodule, and follicular adenoma (43-46). Thyroid carcinomas have been reported to be associated with thyroid nodular lesions (47).

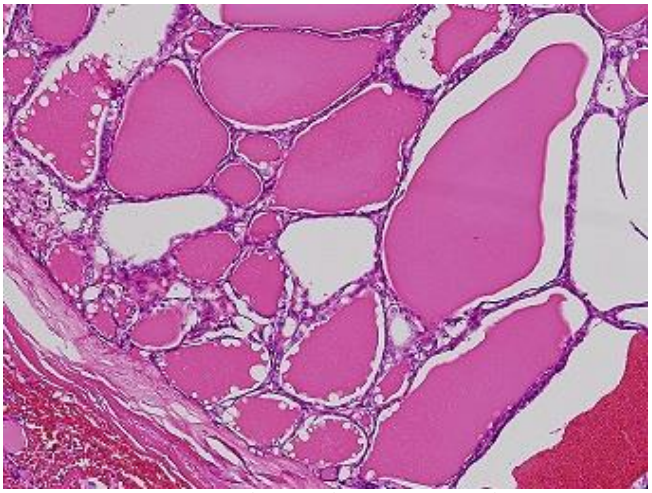

Figure 1: Low-power magnification of a thyroid nodule from a 54-year-old female patient. It is an encapsulated and invasive papillary carcinoma forming macro-follicular structures (Hematoxylin and Eosin stain, x10).

VI. Hyperplastic Adenomatous Nodule, Adenomatous Goiter and Dyshormonogenetic Goiter

Kuma et al. followed 140 patients who had untreated solitary thyroid nodules for an average of about 15 years and they found that majority of the nodules decreased in size (38.3% of nodules disappeared), while 13% of nodules increased in size (16). There were 15 cases with suspicious cytology for PTC and PTC was confirmed in nine cases (including 2 incidental PTCs). The finding of only seven PTCs in 140 thyroid nodules during a 15-year follow-up period (5% in 15 years = 0.33%/year) does not indicate a high risk for thyroid carcinomas compared with latent thyroid carcinomas in autopsy thyroid glands (5-20%) and risk of incidental papillary microcarcinoma (16.7%) in surgically treated thyroid glands for unrelated benign diseases (20, 47, 48).

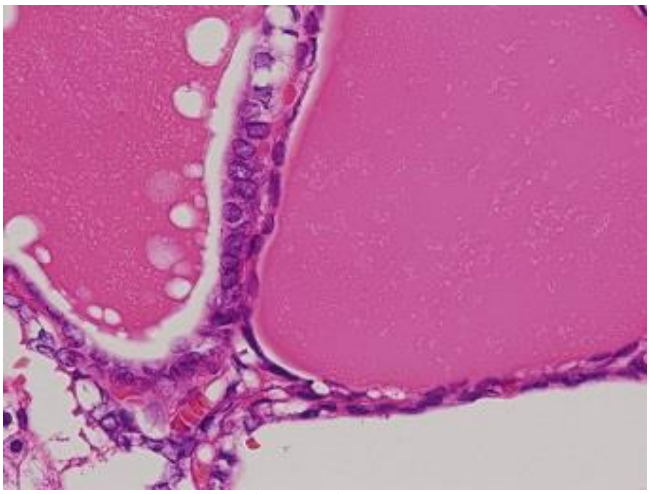

Figure 2: High-power magnification of the Figure 1 demonstrates papillary thyroid carcinoma type nuclear features only in the left field, while follicular cells in the right field contain a small pycnotic nuclus. The two different types of nuclei suggest that PTC cells in the left field may occur or invade in the preexisting thyroid nodule in the right field (Hematoxylin and Eosin stain, x40).

Couch et al. reported that, of the 18 patients with multinodular goiter who demonstrated autosomal dominant inheritance, two patients had PTC (44). There are also some reports of thyroid carcinoma arising in dyshormonogenetic goiter (50-52). Hishinuma et al. reported a high prevalence (7 out of 11) of thyroid carcinoma in patients with thyroglobulin gene mutations and they confirmed activating *BRAF* gene mutations in 2 of the 5 cases examined. They postulated that thyroglobulin mutations predispose to thyroid cancer development through activating mutations of oncogenes, although Ghossein et al. reported only 3 incidental PTCs in 56 cases of dyshormonogenetic goiter (52, 53). Mori et al. reported that the risk of incidental PTC in patients with a benign nodular thyroid lesion was 27.7% and it decreased to 7.22% when clinical cancer was excluded (54). They also found 2 of 20 cases of incidental cancer occurring within a nodule (54). Arora et al. reported that 2% of thyroid malignancy arises within a preexisting benign thyroid nodule (55). Figure 1 is from a 54-year-old female with encapsulated PTC, follicular variant, showing that the tumor contains follicular structures covered with pycnotic small nuclei or large irregular nuclei of typical PTC type nuclear features (Fig 2), as if PTC occurs in the nodule or invades into preexisting AN. Although the incidence of PTC in nodular thyroid lesions is not high, PTC found within a thyroid nodule may indicate that the thyroid nodular lesion may serve as a precursor lesion of thyroid carcinomas. The prevalence of thyroid carcinoma in solitary cold nodule was reported to be from 7.3% to 17%, and from 3.5% to 15% in multinodular goiter in literature (47, 56-58). Fiore et al. analyzed 33,774 patients with cold thyroid nodules and found that the prevalence of PTC increases with TSH, being the highest in patients with serum TSH in the upper limit of the normal range and

the lowest in patients with below normal TSH values (59). They concluded that TSH may have a significant impact on thyroid carcinogenesis and further suggest that thyroid autonomy, by reducing TSH, may slow down cancer progression and reduce the probability that mutated oncogenes may cause clinically detectable cancer (59).

VII. Follicular Adenoma and Atypical Adenoma

Fusco et al. analyzed encapsulated and non-invasive thyroid nodules with borderline morphological features of PTC, so-called well differentiated tumor of uncertain malignant potential (WDT-UMP) or encapsulated follicular variant PTC (60, 61). They concluded that RET activation closely parallels the areas of tumors with cytological alterations and further commented that it is possible that such foci may precede to the development of invasive PTC (60). Arora et al. examined gene expression profiles and clarified that follicular adenomas and Hürthle cell adenomas have similarities to both benign and malignant tumors, suggesting that some of these tumors are premalignant (55, 62). In addition, 10% of surgically excised follicular tumors that are encapsulated follicular lesions with nuclear atypia are WDT-UMP. Arora et al. concluded that these tumors could be precursors of carcinoma (55, 62).

The term "atypical adenoma" has been variably used to refer to FA exhibiting high cellularity, nuclear atypia or unusual histologic patterns (20, 47). Molecular features were analyzed in atypical adenoma, typical adenoma and FTC by Tzen et al. and they concluded that atypical adenoma is a precursor of UC because two cases of atypical adenoma showed a *p53* point mutation in codon 273, a common mutation in various human cancers, including UC (63). However, Revera et al. examined 8 cases of non-invasive encapsulated tumor with high-grade histology and found that these tumors did not recur in a median follow up of 11.9 years, Nikiforova et al. suggested that FA with *PAX8/PPARγ* rearrangements might be non-invasive FTC in which the invasive nature of tumor was overlooked, while Xing et al. commented that the common occurrence of *RAS* mutations in FA, a presumed premalignant lesion, suggests that activated RAS may have a role in early follicular cell tumorigenesis (2, 9, 64). *RET/PTC* rearrangements have been reported in FA, and an association between *RET/PTC* and a high growth rate was recently found (13-15).

VIII. Papillary Microcarcinoma (So-Called Papillary Microtumor)

Papillary thyroid microcarcinoma is defined as PTC of smaller than 1.0 cm in diameter (20). It is a common incidental finding in surgical specimens of the thyroid gland resected for unrelated benign diseases and in autopsy thyroid glands (20, 47, 48). This microtumor is currently labeled as cancer and some have suggested that it may be an early stage in the carcinogenesis of the PTC lineage (12, 65, 66). It occurs in thyroid nodular lesions as a cancer in adenoma (Fig. 1) or in normal looking thyroid as a de novo cancer (Fig. 3).

Papillary microtumors may have lymph node metastasis, recurrence and distant metastasis in a very small number of patients, but the majority of them are indolent in nature (66-73). Some investigators reported their observation trials of patients with this tumor and proved that the majority of papillary microtumors did not grow in size and did not show progression in terms of tumor stage; therefore, immediate aggressive surgical treatment is not necessary for this extremely low-risk thyroid lesion (70, 72). Kakudo et al. proposed a new classification of thyroid follicular cell tumors, in which those biologically benign lesions currently labeled as carcinoma (papillary microcarcinoma, encapsulated PTC, capsular invasion only FTC, WDT-UMP, FT-UMP) are placed in a borderline category between benign and low-risk WDCs (74-77). International experts of thyroid pathology have proposed renaming papillary microcarcinoma as papillary microtumor without using cancer terminology (78).

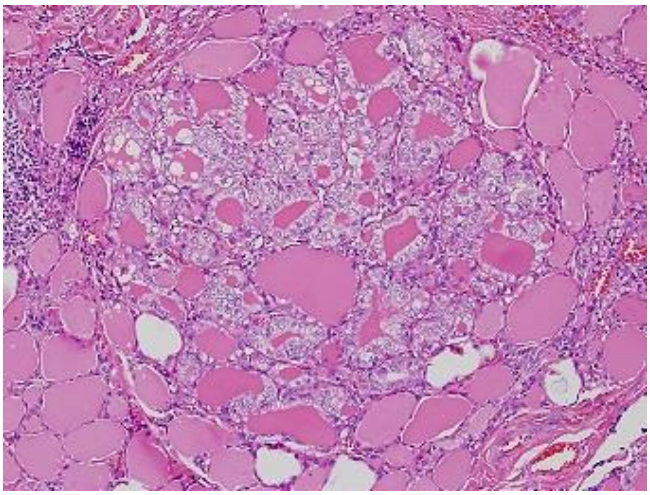

Figure 3: Microscopic papillary carcinoma found in the non-nodular thyroid parenchyma of a 50 years female patient. Papillary carcinoma occurs as if it is de novo cancer. Note papillary thyroid carcinoma type nuclear features, different from normal thyroid in the back ground (Hematoxylin and Eosin stain, x20).

IX. Encapsulated Well-differentiated Thyroid Carcinomas

Most encapsulated thyroid carcinomas in the WDC category, even though they are currently labelled as cancer, are indolent and not life-threatening (74-77, 79-84). Piana et al. collected 108 cases of thyroid carcinoma with capsulation (including FTC and PTC) and found that no tumor-related death occurred for an approximately 12-year follow-up period (84). Sugino et al. and Ito et al. separately analyzed their PTC patients who were treated for benign nodules; surprisingly the disease-free survival rate of those incompletely treated patients was better than that of PTC patients who were radically treated for cancer (80, 81). It has been emphasized in our previous reviews that the encapsulated PTC, WDT-UMP, follicular tumor of uncertain malignant potential (FT-UMP), capsular invasion only FTC, and papillary microcarcinoma, are not genuine cancers in terms of prognosis and may belong to a borderline category (well-differentiated tumor of uncertain behavior) or a precancerous lesion (74-77). Recently, indolent lesion of epithelial origin (IDLE) has been proposed by Esserman et al. for these lesions currently labeled as cancers and their precursors that are unlikely to cause harm if they are left untreated (85). We believe the new concept of IDLE introduced by Esserman and borderline or precancerous lesions in the thyroid tumor classification introduced by our group make it possible to adopt the current knowledge on genetic changes of thyroid carcinomas into the multistep carcinogenesis of thyroid follicular cell tumors, from normal follicular cells to hyperplastic proliferative lesions, precancerous (borderline) benign neoplasia, non-invasive carcinoma, early invasive cancer, invasive cancer with nodal

metastasis, locally advanced cancer, advanced cancer with distant metastasis, PDC, UC and patient death (12).

Conclusions

RET/PTC rearrangements, *PAX8/PPARγ* rearrangements and *RAS* mutations may be found in thyroid neoplasms in both benign and malignant tumors, and these genetic alterations occur as initiation steps rather than as progression events. Additional genetic and epigenetic alterations are required to transform benign precursor lesions into truly malignant thyroid carcinomas. Therefore, *RET/PTC* rearrangements, *PAX8/PPARγ* rearrangements and *RAS* mutations are not firm evidence of malignancy in thyroid cytology and pathology. This is important for the clinical management of patients with thyroid nodules and this borderline category diagnosis will possibly reduce unnecessary surgical treatment for those patients with mutation-positive thyroid nodules. Thyroid nodules with those mutations may be borderline lesions equivalent to tubular adenoma with *APC* mutations in the alimentary tract. Since tubular adenomas with *APC* mutations are histopathologically diagnosed as benign or dysplastic (not cancer) lesions until invasive growth beyond their anatomical structures is identified, thyroid nodules confined to the thyroid gland become borderline lesions and only tumors with extrathyroid invasion or metastasis belong to the malignant category in this diagnostic schema, which has been proposed in our previous studies (74-77).

All of the thyroid lesions discussed in the present review may serve as early steps in thyroid multistep carcinogenesis and we believe that proper identification of these precursor thyroid lesions will help reduce over-diagnosis and over-treatment of patients with thyroid nodules.

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