Papillary Thyroid Carcinoma
An Overview

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- Papillary carcinoma is the most common malignant tumor of the thyroid. It has a variable macroscopic appearance that differs according to the variant microscopic morphologies and the presence or absence of degenerative changes. The histologic variants can be challenging to the pathologist, and some are of clinical significance because of prognostic implications. In this short review, we discuss an approach to papillary carcinoma, the diagnostic dilemmas and controversies, and the ancillary studies that are helpful in resolving them, including immunohistochemistry and molecular studies.

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Thyroid cancer is the most common endocrine malignancy and represents 1% of all malignancies. It is also the most rapidly increasing cancer in women. In 2004, approximately 26,000 new cases of thyroid cancer were recorded in the United States, 75% of them in female patients, and thyroid cancer represented the eighth most common cancer in women. Papillary thyroid carcinoma (PTC) is the most common malignant tumor among all thyroid cancers, comprising an estimated 80% of thyroid cancers. In contrast to the high incidence, death from thyroid cancers, comprising an estimated 80% of thyroid cancers. In contrast to the high incidence, death from thyroid cancer is rare, and most patients respond to surgery and targeted therapy with radioactive iodine.

There are several established risk factors for PTC, including genetic factors, ionizing radiation, and nodular disease of the thyroid. Several genetic syndromes predispose patients to thyroid cancer. Patients with familial adenomatous polyposis develop PTC, usually with distinctive morphologic findings. In Cowden syndrome, patients commonly develop follicular lesion of thyroid, but PTC is also on record with this syndrome. There is also emerging evidence for familial PTC, but the genetic basis of this disorder is as yet unknown.

Several molecular changes are known to underlie PTC, and these are of diagnostic as well as potential prognostic and/or therapeutic significance.

CLINICAL FEATURES

Papillary thyroid carcinoma has diverse clinical presentations. Most commonly it presents as a thyroid nodule that is discovered incidentally or on routine examination. Rarely, patients present with metastasis in a neck lymph node or with hoarseness of voice caused by involvement of the recurrent laryngeal nerve. Distant metastasis as a primary presentation is an exceptionally unusual finding. The investigation of a thyroid nodule commonly includes ultrasound imaging, nuclear scan, and fine-needle aspiration biopsy. The ultrasound is a useful test to distinguish solid from cystic lesions and to identify calcifications. Reading et al reviewed ultrasonographic patterns that are conventionally applied to distinguish benign from malignant thyroid nodules. Among these patterns, 2 are characteristic of PTC. The first pattern is the presence of a solid, hypoechoic nodule with discrete echogenic foci. This diagnosis is further supported by the presence of microcalcification. The second pattern is the solid, hypoechoic nodule with coarse echogenic foci. On nuclear scan, papillary carcinoma is commonly a “cold” nodule; rarely, though, PTC can be a “hot” nodule. It is important to note that uptake of technetium is more common than uptake of iodine, and only the latter predicts a hyperfunctioning lesion associated with suppressed thyrotropin and increased thyroid function.

Fine-needle aspiration biopsy is the single most useful tool in the diagnosis of papillary carcinoma. Fine-needle aspiration biopsy has very high accuracy that reaches more than 95% in satisfactory specimens. The cytologic morphology of PTC is characterized by a cellular aspirate in which the cells are arranged in monolayer sheets of cells, sometimes forming papillae and occasionally having psammoma bodies. The nuclear morphology is characterized by enlarged, overlapped nuclei with powdery chromatin and multiple micronucleoli. The majority of the nuclei have intranuclear grooves. Intranuclear inclusions can be seen.

GROSS PATHOLOGY

A critical component of thyroid diagnosis involves proper handling of thyroid specimens. It is important to distinguish a lobectomy specimen from a hemithyroidectomy specimen that includes the isthmus as well as the lobe. A subtotal thyroidectomy resection includes the lobe containing a dominant lesion, the isthmus, and a significant portion of the other lobe. It can be difficult for the pathologist to distinguish this type of specimen from a
total thyroidectomy. In some cases, the gland will be accompanied by a neck dissection specimen that may include the superior mediastinal contents. When the specimen is received, the different parts should be identified and all parts should be measured and weighed. The external surface is examined for the presence of adhesions, adherent or involved skeletal muscle, and parathyroid glands. The surface should be marked with India ink to determine resection margin involvement by tumor, but there is little rationale for identifying specific margins. The lobes should be serially sectioned from superior to inferior in approximately 0.3-cm-thick sections and examined carefully. The isthmus should be sectioned in the sagittal plane. The thyroid parenchyma should be examined for nodules and cysts. The following features should be documented: multiplicity, circumscription, size, consistency, and color. There is no specific rule for submission of sections; however, if the specimen is small, it can be submitted in toto. If the specimen is too large to do so, representative sections should be taken with consideration of the capsule of the lesion, which is required for evaluation in follicular lesions to determine malignancy.

Papillary carcinoma has different macroscopic morphologies. It may be solid or cystic with papillary excrescences in the classic variant. Solid nodules usually have a tan color and a firm consistency. The oncocytic variant has brown-to-mahogany color. The border of the nodule may be infiltrative or well circumscribed, with or without a capsule, and calcification may be seen. Sclerosis may be a prominent feature. Focal degenerative changes may occur either spontaneously or as a result of previous fine-needle aspiration. These changes include cystic formation, hemorrhage, or necrosis. Therefore, care should be taken when sampling these tumors to consider the periphery of the lesions because they are less prone to degenerative changes.

Multifocal papillary carcinoma appears macroscopically as multiple distinct nodules that are distributed throughout the entire thyroid. Care must be taken in handling such tumors as the measurement of the dominant nodule should be recorded. The appearance is determined by the underlying variant.

### HISTOPATHOLOGY AND VARIANTS

The diagnosis of papillary carcinoma is based on nuclear morphology of a thyroid neoplasm. The existence of multiple architectural variants proves the irrelevance of architecture. The diagnostic nuclear morphology is characterized by the following constellation of features as seen in Figure 1:

1. enlarged and elongated nuclei with crowding and overlap;
2. irregular nuclear contour;
3. chromatin clearing with peripheral margination of chromatin, giving rise to what has been described as *Orphan Annie Eye nuclei*;
4. multiple micronucleoli located immediately underneath the nuclear membrane;
5. nuclear grooves resulting from irregularity of nuclear contour seen in 2 dimensions;
6. intranuclear cytoplasmic pseudoinclusions from the accumulation of cyttoplasm in prominent nuclear grooves.

These features determine the diagnosis. Even in the presence of true papilla formation, lesions that lack the

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*Figure 1.* The nuclear morphology that characterizes papillary thyroid carcinoma includes enlarged, overlapped nuclei that are clear because of the peripheral margination of chromatin, and irregular contours that form grooves and cytoplasmic inclusions (hematoxylin-eosin [H&E], original magnification ×400).

*Figure 2.* Classic papillary thyroid carcinoma is formed of papillae with fibrovascular cores (H&E, original magnification ×100).

*Figure 3.* Follicular variant papillary thyroid carcinoma exhibits scalloping and hypereosinophilia of colloid (H&E, original magnification ×100).
nuclear morphology of papillary carcinoma should be classified as benign papillary nodules, which are known as papillary hyperplastic nodules or follicular adenomas with papillary architecture.2

The classic variant is characterized by complex papillae with thin fibrovascular cores that sometimes become edematous (Figure 2). The papillae are covered by cuboidal and columnar cells with eosinophilic cytoplasm. Psammoma bodies may be also identified and are characterized by purple, laminated calcification.

The follicular variant of papillary carcinoma is characterized by follicular architecture with nuclear features of papillary carcinoma (Figure 3). These lesions are frequently completely circumscribed and therefore are readily mistaken for follicular adenoma. This is an important distinction because these lesions have the potential for metastatic spread; however, the nuclear features can be subtle, leading to variability in the threshold for diagnosis and a high degree of intraobserver variation.8 Apart from nuclear morphology, other morphologic features of this variant of papillary carcinoma include hypereosinophilia of colloid with peripheral scalloping, intrafollicular multinucleate giant cells, and rare psammoma bodies.

The oncocytic variant is formed by cells characterized by abundant eosinophilic and granular cytoplasm caused by mitochondrial accumulation (Figure 4). The cells can be arranged in classic papillae or in follicles, either with microfollicular or macrofollicular architecture.9 The clear cell variant is related to the oncocytic variant, and tumors with clear cells usually have oncocytic cells as well. A subset of oncocytic tumors has striking lymphocytic infiltration of the papillae, resembling Warthin tumor of salivary glands (Figure 5), hence the terminology Warthinlike variant.10

Figure 4. Oncocytic variant of papillary thyroid carcinoma is composed of cells with abundant eosinophilic granular cytoplasm (hematoxylin-eosin [H&E], original magnification ×100).

Figure 5. Warthinlike papillary thyroid carcinoma has a prominent lymphoplasmacytic stromal infiltrate (H&E, original magnification ×200).

Figure 6. Tall cell variant of papillary thyroid carcinoma is characterized by elongated cells that have a height-to-width ratio that exceeds 3:1 (H&E, original magnification ×200).

Figure 7. Cribriform-morular variant of papillary thyroid carcinoma has a characteristic cribriform pattern that is recognized at low magnification (H&E, original magnification ×100).
There is no prognostic significance attributed to these variants of papillary carcinoma; however, other variants do have clinical implications. Papillary microcarcinoma is defined as a papillary carcinoma that measures 1 cm or less in maximum dimension. This variant is very common; in some autopsy series it is reported in up to 35.6% of patients, and in surgical series it is found in up to 24% of total thyroidectomies. The architectural morphology may be classic, follicular, or oncocytic; the variant may be infiltrative or encapsulated. Microcarcinomas are frequently multiple and, when associated with clinically larger and significant papillary carcinomas, they have been considered to represent dissemination of the larger tumor. However, the evidence points to multifocal primary lesions, as shown by diversity of RET/PTC rearrangements and variable X chromosome inactivation. Most experts believe that this lesion, when identified incidentally or as an isolated ultrasound abnormality, is of minimal clinical significance; it has been suggested that they be called papillary microtumor to stay the surgeon’s hand and prevent aggressive management. However, this terminology is not widely accepted. Rarely, these lesions can present with metastatic disease; differences between these rare aggressive microcarcinomas and the usual incidental findings have been described with respect to immunoreactivity for cyclin D1 and p27.

The solid variant is considered to comprise approximately 3% of PTCs. This variant characterized by unencapsulated, invasive borders. The cells are arranged in sheets of cells intervened by fibrous stroma. There are vague papillary formations and the follicular pattern is partly maintained. The nuclear morphology is typical of papillary carcinoma. This variant is associated with aggressive behavior and high frequency of distant metastasis, in comparison with a matched group of the classic variant.

The tall cell variant is an uncommon and infiltrative tumor, considered in some series to represent approximately 10.4% of all papillary carcinomas. It is composed predominantly of cells whose length is at least 3 times their width (Figure 6). The cells usually have abundant eosinophilic cytoplasm and nuclear morphology that is typical of papillary carcinoma. This variant has a significantly higher incidence of extrathyroidal disease, recurrence, and metastases when compared with a matched group of the usual variant of papillary carcinoma from patients of similar age, sex, and date of diagnosis. An extreme variant of this form is the columnar cell variant, which has such stratification of elongated cells that it resembles endometrial carcinoma.

The cribriform-morular variant was first reported in 1994 and was noted to be associated with familial adenomatous polyposis syndrome. This variant is characterized by lobules of tumor separated by fibrous septa. The tumor lobules have cribriform architecture characterized by rigid spaces in the lobules formed by arches of cells with no fibrovascular cores (Figure 7). Spindles cells and squamous morules also can be identified. The pathogenesis of these lesions remains an enigma because they harbor ret/PTC rearrangements that are characteristic of regular papillary carcinoma but show no allelic loss of the intact APC gene, as would be expected in tumors associated with familial polyposis coli. There is a report of a somatic APC gene mutation rather than a germline mutation in one example of this tumor. Although it is rare, the pathologist should be aware of this variant and raise the possibility of underlying APC germline mutations in patients with these variants of PTC.

PITFALLS IN THE DIAGNOSIS

There are certain situations that require caution in evaluating nuclear morphology because of morphologic changes that resemble papillary carcinoma.

Reactive changes following fine-needle aspiration were first described by LiVolsi and Merino, who used the acronym WHAFFT for worrisome histologic alterations following fine-needle aspiration of thyroid. This WHAFFT condition is characterized by nuclear enlargement, chromatin clearing, and micronucleoli that are similar to nuclei of papillary carcinoma. Vascular changes and capsule pseudoinvasion can be seen. However, the distinguishing features are that these findings are located close to a needle tract and associated with hemorrhage, hemosiderin deposition, linear fibrosis, and capsular dehiscence.

In severe chronic lymphocytic thyroiditis, reactive atypia attributed to inflammation results in nuclear morphology similar to that of papillary carcinoma with nuclear enlargement, chromatin clearing, and even grooves. The threshold for nuclear morphology in such cases should be high, and the diagnosis of malignancy should be considered only when there is a discrete nodule with unequivocal architectural changes.

ANCILLARY STUDIES

Immunohistochemistry

Papillary carcinomas are usually easy to diagnose based on the criteria of nuclear morphology within a nodule. However, there are nodules that have subtle nuclear features, and in the absence of invasive behavior, as in well-circumscribed nodules with follicular architecture, the distinction is difficult, but critical, because the differential diagnosis is benign or malignant. In contrast, clearly invasive lesions would be classified follicular or papillary carcinoma, a distinction that is purely academic because the therapy would be the same.

Ancillary tests can help to reach an accurate diagnosis. Several immunohistochemical markers are of some value. Their application to cytology has also been suggested, but there are limitations, as evidenced by the lack of specificity of several markers discussed.

HBME-1 is a monoclonal antibody that was initially promoted as a marker of mesothelial cells; it is directed against an unknown epitope. In the thyroid, HBME-1 is almost exclusively expressed in malignant neoplasms, including papillary carcinoma, whereas benign lesions are negative. HBME-1 is the most specific marker of thyroid malignancy, but it may not be very sensitive because oncocytic lesions are generally negative; also, many malignancies are not stained by this antibody. HBME-1 positivity is characterized by predominantly membranous staining with variable cytoplasmic staining (Figure 8, a).

Cytokeratin 19 is a high-molecular-weight cytokeratin that is a sensitive but not specific marker of papillary carcinoma (Figure 8, b). The sensitivity is highest in classic variant lesions and therefore it may not be helpful where it is most needed, in follicular and oncocytic lesions with nuclear atypia. This marker is also strongly expressed in compressed normal thyroid tissue around lesions, in chronic lymphocytic thyroiditis, and in reactive areas of benign tumors, usually around the site of previous biopsy;
Figure 8.  a, HBME-1 demonstrates strong membranous and cytoplasmic staining in papillary thyroid carcinoma (original magnification ×200). b, The cytokeratin 19 stains papillary thyroid carcinoma with diffuse cytoplasmic staining. Note the adjacent compressed benign follicles also stain with cytokeratin 19, a feature that can be a pitfall.

therefore, its specificity is very poor. However, the presence of widespread positivity for CK 19 in a borderline lesion can be helpful to support the diagnosis of PTC.

Galectin-3 is a member of the lectin family that is expressed by inflammatory and epithelial cells. It has physiologic and pathologic functions including growth regulation, development, differentiation, and cell-cell adhesion. Galectin-3 has been promoted as a marker of malignancy in thyroid; however, its expression in some cases of multinodular goiter and in thyroiditis limits its application. It usually yields cytoplasmic reactivity, and macrophages provide a good internal control.

Molecular Markers

The molecular changes underlying papillary carcinoma have been extensively studied and play an important role in understanding the pathogenesis and the clinicopathologic behavior of the disease. These alterations also may provide diagnostic and prognostic markers that can be applied for accurate diagnosis of borderline lesions and for improvement in the sensitivity and specificity of preoperative cytology.

RET/PTC Rearrangements.—ret is a proto-oncogene that encodes a protein tyrosine kinase receptor with an extracellular domain, a transmembrane domain, and an intracytoplasmic kinase domain. However, ret is involved in a number of rearrangements known as RET/PTC that have been implicated in the tumorigenic process of PTC. There are a number of RET/PTC gene rearrangements, of which RET/PTC1 and RET/PTC3 are the most common. These RET rearrangements are restricted to the thyroid gland and are specific for PTC. The RET/PTC rearrangements are considered to be early events in tumorigenesis, present even at high frequency in microcarcinomas. As such, they serve as sensitive diagnostic markers for controversial lesions, including oncocytic PTC and the rare hyalinizing trabecular tumors, which are now considered to be variants of papillary carcinoma by many pathologists. Their specificity makes them valuable for the cytologic diagnosis of thyroid nodules. In general, they are not thought to be of prognostic value. The diversity of RET/PTC rearrangement may be reflected in the morphology of tumors. For example, in papillary carcinomas of children following radiation exposure from the Chernobyl crisis, RET/PTC3 was associated with solid variant morphology and aggressive behavior.

BRAF Mutations.—BRAF is a protein kinase that has an important role in cell proliferation, differentiation, and programmed cell death. Activating mutations of BRAF were found initially in human colon cancers and malignant melanoma. It is now known that BRAF is also mutated in PTC with high frequency. The most common mutation is characterized by change of valine to glutamate in codon 599, leading to increased kinase activity. The BRAF mutations are associated most often with the classic variant and, because these usually are not diagnostic dilemmas, they usually do not require this ancillary technology, but it can be helpful for nondiagnostic cytology specimens. It appears that BRAF mutations are associated with poorer clinicopathologic outcome resulting from recurrence, but this is controversial.

CURRENT TREATMENT AND PROGNOSIS

Papillary thyroid carcinoma is the most common endocrine cancer. The diagnosis should rely on nuclear morphology rather than architecture. Pathologists should be
aware of different variants because some of these variants have clinical significance. Ancillary studies, including immunohistochemical stains and molecular detection of gene rearrangements and point mutation, are of value in cytology and for the correct classification of borderline lesions. The challenge that remains is distinguishing the common lesions that likely do not require aggressive radioactive iodine therapy from the minority of PTCs that will recur and metastasize. At present, patient management relies only on a uniform approach to almost all lesions with this diagnosis, but prognostic markers have been suggested. Future studies should be directed at identifying features that will determine more rational algorithms to guide patient care.

References