

# Educational Case: Thyroid Neoplasms: Pathogenesis, Diagnosis, and Treatment

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*The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see <http://journals.sagepub.com/doi/10.1177/2374289518777471>.*

## Keywords

pathology competencies, organ system pathology, endocrine, follicular adenoma, follicular carcinoma, papillary thyroid carcinoma, thyroid neoplasms

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## Primary Objectives

**Objective EN5.1: Thyroid Neoplasms.** Compare and contrast the clinicopathologic features of follicular adenomas, follicular carcinoma, and papillary thyroid carcinoma.

Competency 2: Organ System Pathology; Topic EN: Endocrine; Learning Goal 5: Endocrine Neoplasms.

## Patient Presentation, I

A 30-year-old female presents with a palpable right thyroid nodule. The nodule was first noticed 3 months ago and has increased in size slightly over time. The patient denies having hoarseness, dysphagia, weight changes, intolerance to cold or hot weather, drowsiness, or palpitations. A serum thyroid-stimulating hormone (TSH) test was performed, and it was within normal limits. Ultrasonography (US) of the thyroid revealed a solitary well-circumscribed nodule on the right lower lobe of the thyroid measuring  $2.0 \times 1.5 \times 1.0$  cm.

## Diagnostic Findings, Part I

### What Is Your Differential Diagnosis Based on the Clinical History?

Palpable thyroid nodules can be found in 5% of women and 1% of men.<sup>1</sup> The prevalence can increase to 20% to 70% if

nonpalpable nodules are included, and these are usually detected by ultrasound or autopsy.<sup>2</sup> Around 7% to 15% of all nodules are thyroid cancers<sup>1</sup>; therefore, thyroid nodules should be evaluated accordingly. The differential diagnosis for a thyroid solitary nodule with a normal TSH in decreasing order of frequency is hyperplastic nodule, follicular adenoma, papillary thyroid carcinoma (PTC), and follicular carcinoma. Other neoplasms are much less frequent.

## Questions/Discussion Points, Part I

### What Testing Is Available for This Patient and Which Is Recommended?

As per the 2015 American Thyroid Association Management Guidelines, nodules greater than 1 cm should be further evaluated.<sup>1</sup> Serum TSH levels can be measured. If the TSH of the patient is low, a radionuclide (preferably <sup>123</sup>I) thyroid scan should be performed to document whether the

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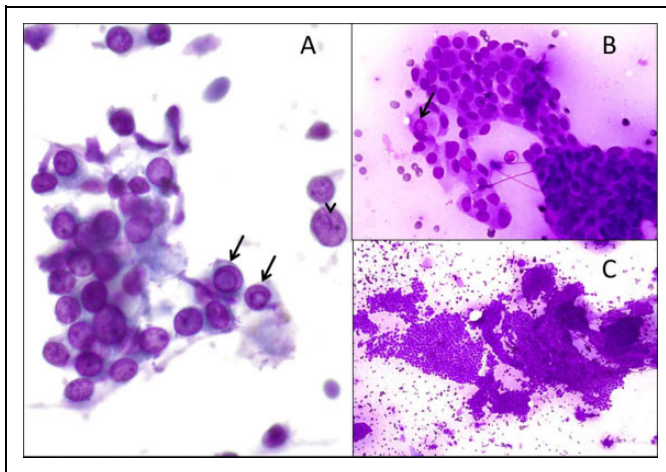
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**Figure 1.** A and B, Cytology of thyroid fine needle aspiration (FNA) showing papillary thyroid carcinoma (PTC) nuclear changes: grooves (arrowhead), intranuclear pseudoinclusions (arrow), nucleoli, and powdery chromatin, as well as nuclear crowding and nuclear enlargement (A, PAP stained, high-power 60 $\times$  magnification, B, Diff quick-stained intermediate power 40 $\times$  magnification). C, A papillary formation is observed. (diff quick stained, low power 10 $\times$  magnification).

nodule is hyperfunctioning (“hot”), isofunctioning (“warm”), or nonfunctioning (“cold”).<sup>1</sup> Hyperfunctioning nodules rarely harbor malignancy.<sup>1</sup>

Thyroid US is considered the imaging modality of choice for the investigation of thyroid nodules. Several features are assessed with the US, including number, size, margin, contours and shape of the nodule, cystic or solid nodule, vascularity, and presence of calcifications, among others. Individual US features may have limited value distinguishing between benign and malignant thyroid nodules, but when multiple signs of malignancy appear in combination, it is possible to make an accurate prediction. Some of the US features suggestive of malignancy are ill-defined nodule, irregular margins, hypervascularity, microcalcifications or coarse calcifications, solid and hypoechoic nodule, and invasion of surrounding tissue.<sup>3</sup>

A fine needle aspiration (FNA) biopsy will be the procedure of choice in the evaluation of a thyroid nodule larger than 1 cm.<sup>1</sup> Nodules smaller than 1 cm are not usually biopsied unless they have sonographically suspicious features or other risk factors for malignancy, such as history of thyroid cancer and radiation exposure, among others.<sup>2</sup> Fine needle aspiration is the most cost-effective and least invasive procedure that will help guide the management and treatment of a patient. Fine needle aspiration can be performed either with palpation or under ultrasound guidance, depending on the location of the nodule or how difficult it is to palpate or properly fix the target.

## Diagnostic Findings, Part 2

The patient underwent an US-guided thyroid FNA biopsy. Microscopic examination of the smears stained by Papanicolaou method showed clusters and papillary fragments of

follicular cells with nuclear enlargement, pale nuclei, powdery chromatin, nuclear pseudoinclusions, and nuclear grooves (Figure 1).

## Based on the Cytological Findings, What Is the Correct Diagnosis?

The smears showed the classic cytologic features of a PTC, malignant (Bethesda VI). Since the risk of malignancy for this lesion is 94% to 99%, a near total thyroidectomy or lobectomy is indicated for this patient.

## What Is the Bethesda System and How This Can Aid in the Management and Treatment of the Patient?

The Bethesda System for Reporting Thyroid Cytology (BSRTC) is a set of recommendations on how to report thyroid cytology specimens in diagnostic categories with associated risk of malignancy and patient management (Table 1<sup>4</sup>). It is a consensus on terminology and morphologic criteria that aims to facilitate communication among the different disciplines in clinical medicine and pathology.

Using the BSRTC, a diagnosis of malignancy (PTC) on FNA is made whenever the cytomorphologic features are conclusive for malignancy. The criteria for reporting PTC are follicular cells arranged in papillae (fibrovascular cores) or syncytial monolayers with the characteristic nuclear features such as enlarged oval or irregular nuclei, nuclear crowding, longitudinal nuclear grooves, intranuclear cytoplasmic pseudoinclusions, pale nuclei with powdery chromatin, and psammoma bodies (not always present).

## Questions/Discussion Points, Part 2

### What Are the Clinical Presentation and Biologic Behavior of PTC?

Papillary thyroid carcinoma usually presents as a solitary, painless nodule, and around 30% of patients might also have associated lymphadenopathy.<sup>5</sup> It tends to grow very slowly and usually involves only 1 thyroid lobe. In large tumors, the presentation will include dysphagia, stridor, and cough.<sup>5</sup> In some cases, these neoplasms are discovered incidentally during the workup of a different problem.<sup>5</sup>

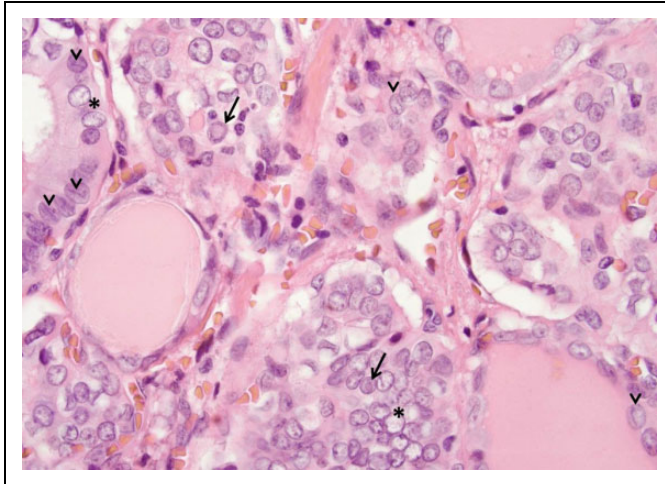
Papillary thyroid carcinoma is the most common thyroid cancer and accounts for approximately 80% of malignant neoplasms of the thyroid with a female to male ratio of 4:1.<sup>2,5</sup> It is associated with radiation exposure and its incidence is higher in areas with high iodine intake.<sup>5</sup>

### Describe the Pathological Features of PTC

The gross pathology is variable from well-circumscribed nodule to diffuse involvement of the lobe, or multifocal.<sup>5</sup> The cut surface is white-gray, firm, and granular with possible presence of calcifications.<sup>5</sup> The microscopic histologic features are similar to the

**Table 1.** The Bethesda System for Reporting Thyroid Cytology Diagnostic Categories.<sup>4</sup>

| Diagnostic Category   | Risk of Malignancy (%) | Management                                  |
|---|------------------------|---|
| I Nondiagnostic or Unsatisfactory   | 5-10                   | Repeat FNA with ultrasound guidance         |
| II Benign   | 0-3                    | Clinical and sonographic follow-up          |
| III Atypia of uncertain significance or Follicular lesion of uncertain significance | ~ 10-30                | Repeat FNA, molecular testing, or lobectomy |
| IV Follicular neoplasm or Suspicious for a follicular neoplasm                      | 25-40                  | Molecular testing, lobectomy                |
| V Suspicious for malignancy   | 50-75                  | Near total thyroidectomy or lobectomy       |
| VI Malignant  | 97-99                  | Near total thyroidectomy or lobectomy       |

**Figure 2.** Histology of papillary thyroid carcinoma (PTC) showing nuclear changes: chromatin clearing known as “Orphan Annie eye” nuclei (asterisk), grooves (arrow head), intranuclear pseudoinclusions (arrow), nucleoli, powdery chromatin, crowding, and overlapping (H&E stained, high power 60× magnification).

cytologic features. The papillary structures are more evident and contain complex branching true papillae with fibrovascular cores.<sup>5</sup> The neoplastic cells will show the classic chromatin clearing called “Orphan Annie eye” nuclei (Figure 2A).<sup>5</sup> There are different variants of PTC (classic or usual, microcarcinoma, follicular variant, diffuse sclerosing variant, cribriform-morular variant, oncocytic variant, tall cell variant, columnar cell variant) and their microscopic characteristics will vary slightly from the classic PTC; however, they must present the characteristic nuclear features (Figure 2B).<sup>5</sup> The classic or usual variant is the most common presentation of PTC, representing ~75% to 80% of cases.

### What Genetic Mutations Does This Neoplasm Harbor?

Papillary thyroid cancers frequently have genetic mutations and rearrangements that lead to activation of the mitogen-activated protein kinase that promotes cell division.<sup>6</sup> In PTC, the most commonly identified mutations in this pathway are point mutations of the *BRAF* and *RAS* genes and *RET/PTC* rearrangement, found in >70% of cases.<sup>6</sup> The most common genetic alteration is the *BRAF* point mutation (V600E), identified in ~45% of PTC cases.

Genetic alterations involving the tyrosine kinase signaling pathways (*RET/RAS/RAF* pathway) are interconnected with the epidermal growth factor receptor activation cascade, which leads to the syntheses of vascular endothelial growth factor (VEGF) and VEGF receptor, which has also been found in PTC, particularly in tumors with *BRAF* mutations. Drugs targeting these pathways could play a significant role in controlling the progression of the disease.

### How Is Molecular Testing Useful in Management of Thyroid Nodules?

Approximately 10% to 15% of thyroid nodules on FNA fall into the indeterminate category which includes follicular and oncocytic neoplasms (Bethesda IV) and atypia of undetermined significance/follicular lesion of undetermined significance (Bethesda III), according to the most current categorization.<sup>4</sup> For these cases, molecular testing is recommended for management since thyroid cancers are commonly associated with specific molecular alterations.

### What Are the Treatment Options for Thyroid Cancer?

Treatment options for thyroid cancer include surgery, radioactive iodine (<sup>131</sup>I) ablation (RAI), molecular-targeted therapies with several tyrosine kinase inhibitors, and external beam radiation. Surgery is the treatment of choice; however, the extent of the surgery is still controversial (total thyroidectomy vs near total thyroidectomy vs. lobectomy).<sup>5</sup> Lymph node sampling can be performed if there is clinical or radiographic enlargement. The most common complications after surgery are damage to the recurrent laryngeal nerve and hypoparathyroidism. The postoperative disease status can be evaluated with postoperative serum thyroglobulin and/or ultrasound.<sup>1</sup>

Radioactive iodine is used in coordination with thyroidectomy to completely ablate the thyroid gland and to eradicate possible residual cancer. The first-dose administration is referred to as ablation, whereas subsequent administrations for residual disease is referred to as treatment.<sup>3</sup>

Tyrosine kinase inhibitors, which primarily target angiogenesis (specifically VEGF receptor signaling pathways), are used to treat patients with recurrent or metastatic thyroid cancers who do not respond to RAI and TSH-suppressive



hormone therapy.<sup>3,7</sup> Two drugs, Sorafenib and Lenvatinib, are approved by the Food and Drug Administration for use in selected patients with refractory metastatic differentiated thyroid cancers.

External beam radiation therapy is only used for palliative treatment of patients with advanced or inoperable thyroid cancer and it may be administered in the adjuvant setting, after surgical resection, or as primary treatment. It is usually considered in patients over 45 years of age who have grossly visible extrathyroidal extension and a high likelihood of residual disease during surgery, and it is also reserved for tumors that are unresponsive to RAI.<sup>3</sup>

### What Is the Prognosis of Patients With PTC?

In general, PTC is indolent and has an excellent prognosis.<sup>2,5</sup> The 10-year survival rate is greater than 90%.<sup>2</sup> Although the prognosis is excellent, certain clinical and pathologic features have been identified that portend a somewhat higher risk of tumor recurrence and cancer-related mortality, including over 45 years of age, male gender, size of carcinoma being greater than 2 cm<sup>3</sup>, invasion into surrounding tissue, histological subtype, and distant metastasis. It spreads mostly by lymphatic channels and metastasis to lymph nodes is frequent; however, this does not affect prognosis.<sup>5</sup>

The histological subtypes of PTC associated with worse prognosis are tall cell, insular, and hobnail variants. Patients with aggressive histologic subtypes are usually treated more aggressively.<sup>8</sup> In addition to its strong correlation with PTC, the *BRAF* V600E mutation has also been associated with poor prognosis and higher recurrence rate.

### Patient Presentation, 2

A 55-year-old woman presents with a painless, slowly enlarging left thyroid mass. A previous FNA of the lesion was reported as suspicious for a follicular neoplasm (Bethesda IV). Following this diagnosis, the patient underwent a total thyroidectomy.

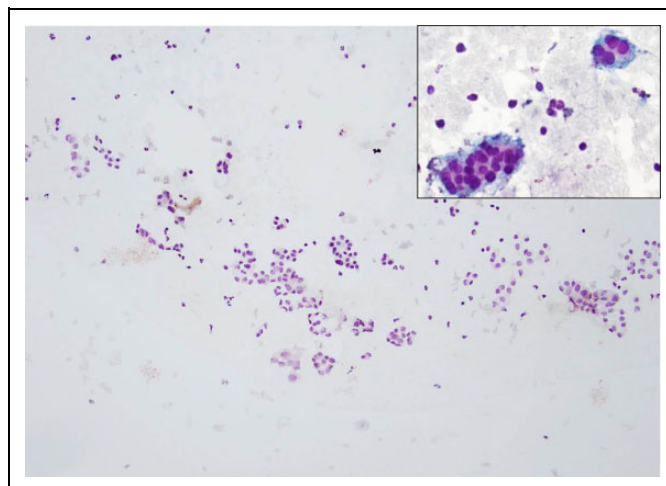
### Diagnostic Findings, Patient 2

On gross examination, there is a solitary encapsulated mass, measuring 3 cm in greatest dimension. Microscopically, the tumor is surrounded with a capsule (encapsulated) and shows a microfollicular pattern. Upon thorough examination of the capsule, an area where the tumor cells penetrate through the whole thickness of the capsule was found. This is referred as capsular invasion; therefore, a diagnosis of follicular carcinoma was reported.

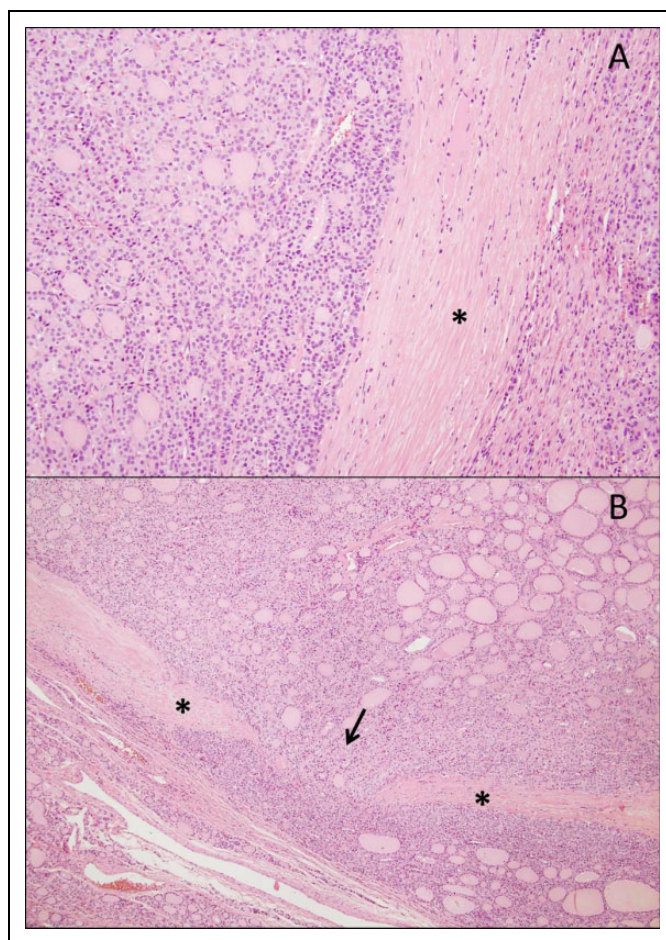
### Questions/Discussion Points, Patient 2

#### What Are the Cytologic and Pathologic Features of Follicular Carcinoma?

The cytomorphology on FNA specimens will show a marked cellularity, consisting predominantly of small clusters of



**Figure 3.** Cytology of thyroid fine needle aspiration (FNA) showing microfollicles of a follicular neoplasm (PAP stained, low power 10 × magnification). Papillary formations as seen here are composed of follicular cells surrounding a fibrovascular core.



**Figure 4.** A, Histology of follicular adenoma showing a fibrous capsule (asterisk) and a microfollicular pattern on left side of image (H&E stained, intermediate power 40× magnification). B, Evident capsular invasion (arrow) is present in follicular carcinoma. Capsule is shown with asterisks (H&E stained, intermediate power 40× magnification).

follicular cells called microfollicles, with scant colloid in the background (Figure 3). The cytology of adenoma and carcinoma can be almost identical, so they are both diagnosed as suspicious for a follicular neoplasm (Bethesda IV).

The distinction between the 2 is made by examining the capsule for invasion after resection. The resection specimen of follicular adenoma and carcinoma will show a fibrous capsule grossly and a microfollicular pattern microscopically (Figure 4A).<sup>5</sup> These lesions will lack the characteristic nuclear features of PTC.<sup>5</sup> To differentiate a follicular adenoma from a carcinoma, evident capsular invasion must be present (Figure 4B). This distinction is only diagnosed on the resected specimen, and thorough examination of the capsule is required. In follicular carcinomas, the most common alterations include *RAS* mutations and *PAX8-PPAR $\gamma$*  rearrangement.<sup>6</sup> Many of these mutations are being explored as therapeutic targets for thyroid cancer.<sup>6</sup>

Follicular adenomas are treated with lobectomy and have an excellent long-term prognosis.<sup>5</sup> The treatment of choice for follicular carcinoma is surgery (lobectomy or thyroidectomy). A lobectomy is more likely to be performed in younger patients (<45 years), with a single nodule (<40 mm), and without thyroiditis or metastatic disease.<sup>5</sup> Radioactive iodine therapy can be indicated in patients with lymph node metastasis who underwent total thyroidectomy. Follicular carcinoma has an excellent long-term prognosis on minimally invasive lesions, 97% 20-year survival and a 50% 20-year survival on widely invasive lesions.<sup>5</sup>

## Teaching Points

- Thyroid nodules are a common finding, and only 7% to 15% are malignant.
- Papillary thyroid carcinoma is the most common thyroid malignancy and presents with characteristic nuclear features on microscopic examination.
- The BSRTC is a guideline to create uniformity in reporting thyroid lesions on FNA.

- Most common mutation of PTCs is the point mutations of the *BRAF* gene.
- To differentiate a follicular adenoma from a follicular carcinoma, a thorough examination of the capsule should be done to assess capsular invasion.

## Declaration of Conflicting Interests

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