Educational Case: Cytology for Staging Neoplasia and Thyroid Neoplasms

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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/10.1177/2374289517715040.

Primary Objective

Objective CYP1.4: Use of Cytology for Staging Neoplasms. Describe how cytologic specimens can add valuable information for tumor staging.

Competency 3: Diagnostic Medicine and Therapeutic Pathology; Topic CYP: Cytopathology; Learning Goal 1: Cytologic Diagnosis.

Secondary Objective

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

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

Patient Presentation

A 28-year-old, otherwise healthy, Caucasian male presents to his family physician with a 3 cm swelling of his right lateral neck. He has no significant past medical history. On physical examination of the neck, the swelling is inferior to the thyroid and lateral to the carotid, soft and somewhat fluctuant, suggesting a cystic lesion, while a solid component is not appreciated

with palpation. Adenopathy in the neck is not noted, and the salivary glands on examination are within normal limits. The right thyroid lobe is mildly enlarged, but a discrete mass is not appreciated by palpation. The patient is referred to the local hospital radiology department for neck ultrasound and biopsy.

Diagnostic Findings, Part 1

Ultrasound revealed the 3 cm swelling in the lateral neck is largely cystic with a 1 mm wall thickness, with a 6 mm solid nodule along one side. Ultrasound of the thyroid reveals a 12 mm nonspiculated and well-circumscribed lesion in the right lobe. The radiologist performs a fine needle aspiration biopsy (FNAB) of the right lateral neck mass, aspirating 7 mL of reddish brown slightly turbid fluid, and then performing 2 additional passes of the solid 6 mm area. Rapid on-site

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evaluation by the pathologist indicates diagnostic tissue was obtained, and additional passes were not necessary.

Questions/Discussion Points, Part 1

What Is the Clinical Differential Diagnosis for This Patient's Neck Mass?

A neck mass can arise from different tissue origins including the thyroid gland, salivary glands, lymph nodes, and soft tissues. Lesions of thyroid origin can include hyperplasia, thyroiditis, and benign or malignant thyroid neoplasia. Lesions of salivary gland origin can include sialadenitis and benign or malignant salivary gland neoplasia such as pleomorphic adenoma, Warthn tumor, or mucoepidermoid carcinoma. Lesions of lymph node origin can include reactive adenopathy, lymphomas, and metastatic carcinomas. Soft tissue origin can include lipoma or paraganglioma. There are 3 major etiologic categories for the classification of neck masses: congenital, inflammatory/infectious, and neoplastic. Clinical findings can point the physician to one of these 3; however, tissue biopsy is necessary for confirmation of the origin and diagnosis of the lesion. In a very young child without evidence of inflammation/infection (redness, pain, and warmth), consider congenital lesions first. In an acquired lesion in patients over 45 without evidence of inflammation/infection, consider neoplasia first. The differential diagnosis for a possibly cystic mass in the neck includes abscess, thyroglossal duct cyst (midline), branchial cleft cyst (lateral), lymphangioma, Warthin tumor (parotid), and metastatic cystic neoplasms to neck lymph nodes such as cystic head and neck squamous cell carcinoma, mucoepidermoid carcinoma, and cystic papillary thyroid carcinoma (PTC).[1]

Cytology for Staging Neoplasia

How do cytology specimens add valuable information for tumor staging? The extent and spread of a primary carcinoma, known as tumor stage, is critical in defining prognosis, treatment, and eligibility for clinical trials. The most commonly used system is the tumor, node, and metastasis (TNM) system as defined by the American Joint Commission on Cancer (AJCC) and the Union for International Cancer Control. A cancer is thus classified based on the primary tumor size and extent (T), regional lymph node involvement (N), and presence or absence of distant metastasis (M). This staging can be based on clinical findings (cTNM), or the clinical stage is modified by the pathologic examination of the resected tumor and regional lymph nodes and is then referred to as the pathologic stage (pTNM).[2]

With regard to staging thyroid gland cancer, evaluation of neck lymph nodes is important and accessible to cytologic diagnosis by FNAB, particularly as in this case when a patient presents with a clinically abnormal node. In this patient, based on the FNAB result and lateral location of the node, we know that he is pN1b in the current TNM staging system,[2] and clinically his primary tumor seems to be greater than 1 cm but less
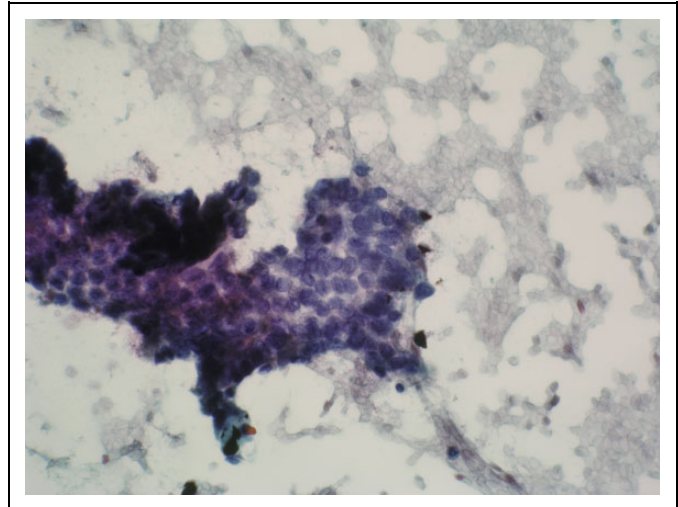

Figure 1. Direct smear from the fine-needle aspiration of the lateral neck mass. Papanicolaou stain at ×400 showing the classic papillary-shaped group of thyroid epithelium with pale chromatin, oval nuclei with longitudinal grooves, and nuclear crowding and overlap.

than or equal to 2 cm and would be cT1b. The precise pathological T stage of the primary tumor will be determined by the surgical pathology examination of the excised thyroid gland. If this patient were to have a lesion in a common site of metastatic thyroid cancer (lung or bone), these would also be amenable to cytologic diagnosis by radiologic-guided FNAB, using cytology to complete his nodal and distant metastasis staging, even prior to definitive surgical treatment.

Thyroid cancer is not the only tumor type where cytologic diagnosis plays a role in staging a patient with a malignant neoplasm. Fine needle aspiration biopsy is used for diagnosing lymph node metastasis in head and neck squamous cell carcinoma. Endoscopic ultrasound-directed FNAB is used for primary diagnosis and lymph node staging of upper gastrointestinal tract, pancreatic, and lung carcinomas as well. Pleural fluid cytology, when positive in a patient with lung cancer, is diagnostic of pM1a in the TNM staging system. Likewise, a positive pleural fluid cytology in a patient with a carcinoma below the diaphragm would designate the patient as a pM1, for example, in a woman with a primary ovarian cancer. Image-guided FNAB is commonly used to confirm liver metastasis, with colon as a common primary site spreading to the liver. Besides staging, cytologic FNAB can also give important information about prognosis and direct treatment. Thus, in children with acute lymphoblastic leukemia (ALL), positive cerebrospinal fluid cytology is an adverse prognostic finding associated with worse outcome.[2] In adults with ALL, positive cerebrospinal fluid cytology requires directed therapy but does not appear to impact overall prognosis.

Describe the cytologic findings in the fine needle aspiration biopsy as they relate to the differential diagnosis of this neck mass. A representative portion of the FNAB smear is shown (Figure 1). There are insufficient neutrophils for a diagnosis of an abscess
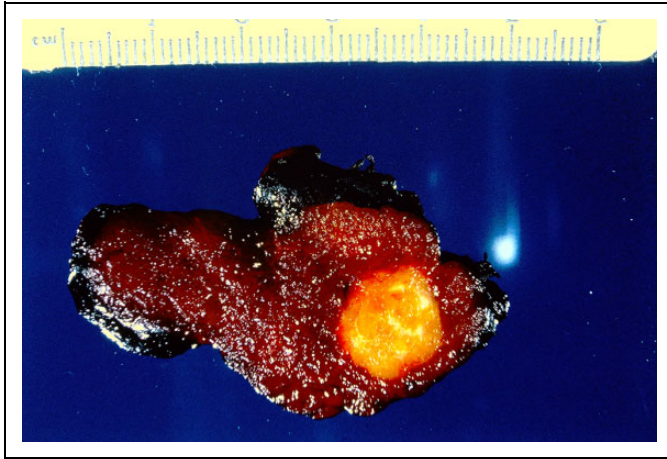
Figure 2. Gross pathology of the thyroid excision, showing a 1.2 cm circumscribed but not encapsulated tan mass surrounded by dark red normal appearing thyroid tissue. The thyroid capsule/margin is inked black for identification on the histologic slides. Tumor does not grossly extend beyond the thyroid gland.

or other acute inflammatory process. There are insufficient lymphocytes for a consideration of reactive adenopathy or lymphoma. Soft tissue components such as adipose tissue are absent. The smear does show an atypical epithelial group, and the reported background lymphocytes would be consistent with a cystic nodal metastasis. The presence of nuclear overlap, pale chromatin, nuclear grooves, and staghorn shape of the cell group are typical of PTC. A follicular neoplasm such as follicular adenoma (FA) or follicular carcinoma (FC) typically has small microfollicular groups, dark chromatin, and round nuclei. Thyroid FNAB cytology cannot reliably distinguish FA from FC, and both are usually classified as a follicular neoplasm without further distinction on FNAB. However, any thyroid epithelium in the neck lateral to the great vessels should be considered malignant. The final cytopathologic diagnosis for this patient is "positive for metastatic PTC with background lymphoid tissue, consistent with a cystic nodal metastasis."

Diagnostic Findings, Part 2

The patient is referred to a head and neck surgeon for surgical treatment. A right thyroid lobectomy is performed.

Describe the Gross Features of the Lesion Found in the Right Lobectomy Specimen

There is a 12 mm lesion identified which appears well circumscribed, but not encapsulated (Figure 2). This is a solitary nodule and is yellow and firm on the cut surface. The stellate pale areas in the lesion are very firm, possibly representing fibrous scarring. This gross appearance could be seen with FA, FC, PTC, or medullary carcinoma (MC) among the common primary thyroid lesions.

Describe the Histologic Features of the Tumor

The histology shows no well-formed follicular architecture removing FA and FC from your differential diagnosis (Figure 3). There is well-formed papillary architecture which would not be seen with MC. The cytologic features are similar to those in the FNAB leading to the final diagnosis of PTC.

An intraoperative frozen section confirms PTC, classic type. A completion left lobectomy with isthmus is performed, as well as a central and right neck dissection. On pathologic examination, the papillary carcinoma is found to be within 2 mm of the thyroid gland capsule, and gross extrathyroidal extension is not present. Five of 18 total nodes are positive for PTC in neck zones III and IV. Thus, this patient has a pT1b tumor based on the size (>1 cm and <2 cm) and lack of gross extrathyroidal disease. The lymph nodes are pN1b based on the involvement of the lateral nodes (levels III and IV), and the M stage is not able to be assessed pathologically.

Questions/Discussion Points, Part 2

Compare and Contrast the Clinicopathologic Features of Follicular Adenomas, Follicular Carcinoma, and Papillary Thyroid Carcinoma Beginning With Papillary Thyroid Carcinoma. First, What Morphologic Features Are Characteristic for Papillary Thyroid Carcinoma and Separate It From Follicular Neoplasms?

The defining morphologic features of PTC are largely nuclear cytologic features including pale nuclear chromatin, oval nuclei with longitudinal nuclear grooves, small peripherally placed nucleoli, and the presence of intranuclear pseudoinclusions. The pale chromatin has been described as optically clear, ground glass, empty, or Orphan Annie eye nuclei. These cytologic features of PTC are all readily recognized on cytology smears (Figure 1), and thus unlike FC, PTC is readily diagnosed on FNAB cytology. In contrast, follicular neoplasms (FA and FC) tend to have round rather than oblong nuclei, darker and coarser chromatin (Figures 4 and 5), and do not show grooves or pseudoinclusions. In addition, rather than microfollicles with a small plug of central colloid (FA and FC), classic PTC is characterized by the malignant epithelium on delicate finger-like papillae with a central fibrovascular core (Figure 3). Psammoma bodies within the papillae are common and may be seen as tiny calcifications on imaging. However, a follicular variant of PTC exists with a microfollicular architecture similar to FA and FC. This follicular variant of PTC can be widely invasive or encapsulated with capsular and or vascular invasion, and the typical PTC cytology is present (Figure 6) even in the absence of well-formed papillary structures (Figure 3). An encapsulated neoplasm of follicular architecture with the cytomorphology of PTC in the absence of capsular and vascular invasion behaves in an indolent nonmalignant fashion similar to FA and, in the most recent World Health Organization (WHO), is classified as a noninvasive follicular thyroid neoplasm with papillary-like nuclear features.[3] The diagnosis of
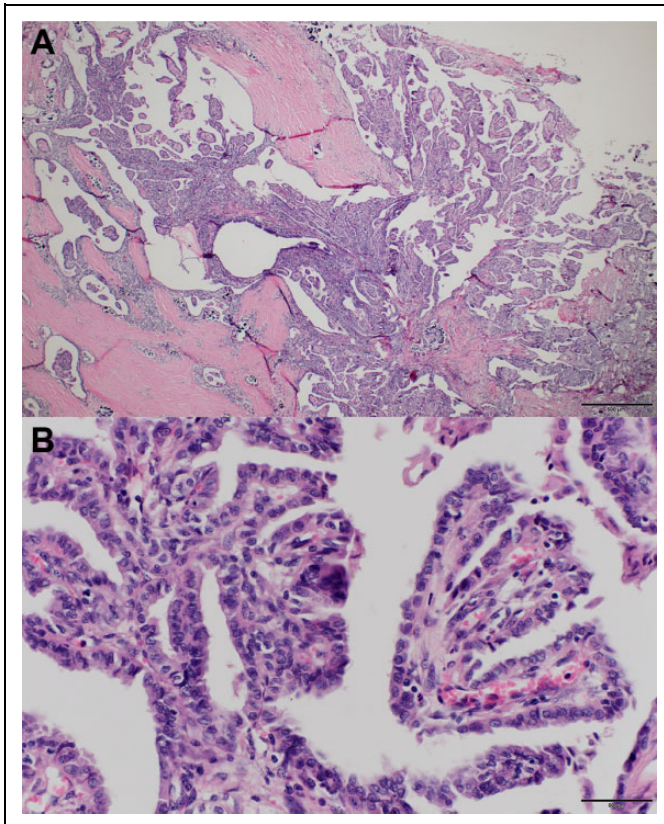
Figure 3. Papillary thyroid carcinoma, classic type with well-formed finger-like papillae with central fibrovascular cores. Nuclei show pale chromatin, oval nuclei with longitudinal grooves, and small peripheral nucleoli. A, ×40, scale bar 500 μm. B, ×400, scale bar 50 μm.

noninvasive follicular thyroid neoplasm with papillary-like nuclear features requires complete histologic evaluation of the nodule to exclude foci of papillary architecture and capsular or vascular invasion. The WHO also includes "follicular tumor of uncertain malignant potential" and "well-differentiated tumor of uncertain malignant potential" in the 2017 classification for tumors with questionable features of capsular and vascular invasion[3] after complete histologic examination.

Summarize the Main Clinical Prognostic Features of Papillary Thyroid Carcinoma

Papillary thyroid carcinoma accounts for about 85% of primary thyroid cancers and in general is associated with an excellent prognosis, with a 95% 10-year survival rate; however, 5% to 20% may have a local or regional recurrence and 10% to 15% distant metastasis. Papillary thyroid carcinoma frequently spreads through lymphatics and neck adenopathy can be seen. Presentation of patients older than 55 years is an adverse prognostic factor, and the AJCC stage groups reflect this as all pN1 is stage group I in patients younger than 55, but stage group II in patients 55 and older. Any pT, any pN, and M1 is stage group II in patients under age 55, but stage group IVB over age 55.[2] In addition, there are some histologic variants of PTC associated with more aggressive behavior. The tall cell variant of PTC
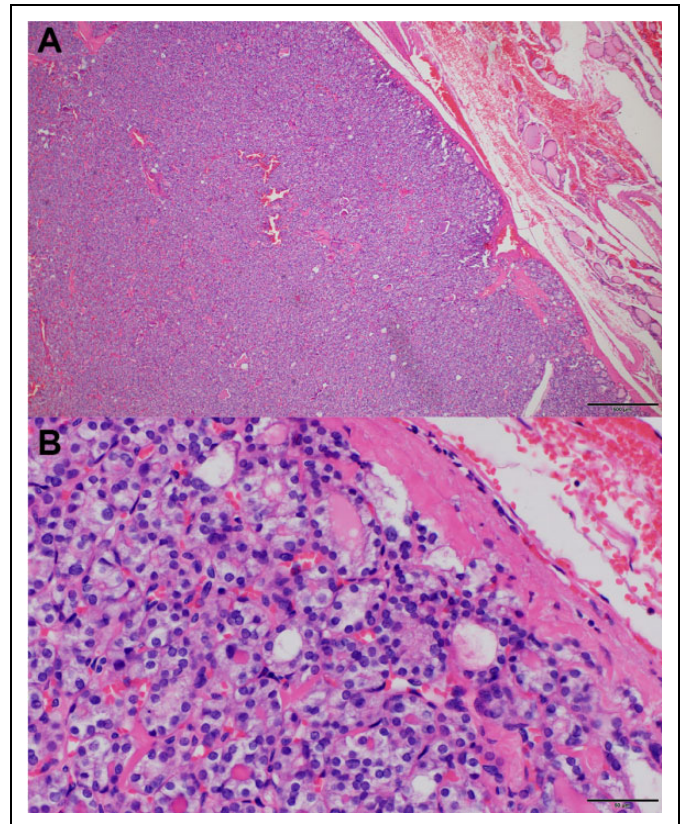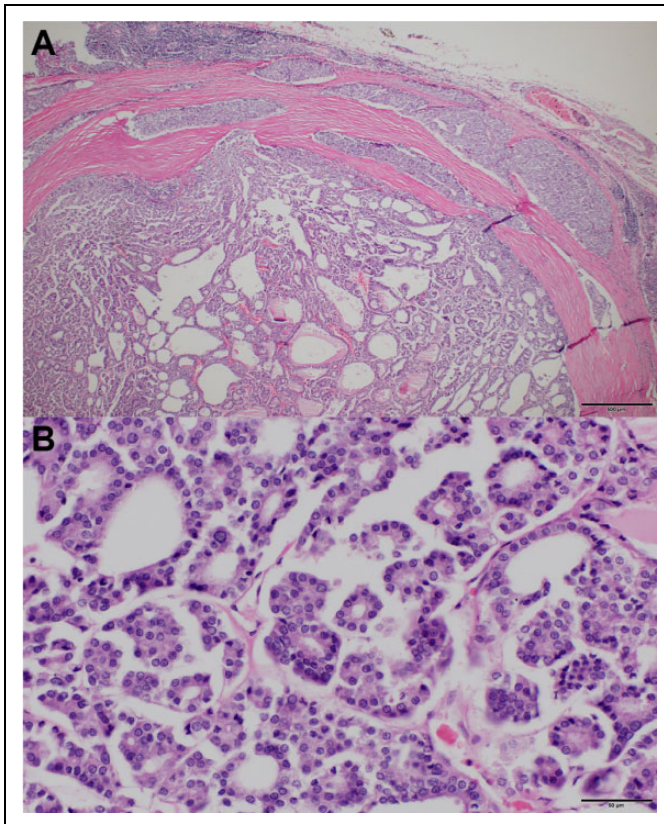

Figure 4. Follicular adenoma showing a proliferation of small follicles with limited colloid (microfollicles) with a well-formed fibrous capsule and no evidence of capsular or vascular invasion. Chromatin is dark and nuclei are round. A, ×40 scale bar 500 μm. B, ×400 scale bar 50 μm.

occurs at older ages than classic PTC and more often presents with gross extrathyroidal extension, vascular invasion, and metastasis than does classic PTC. The tall cell variant of PTC also tends to be resistant to radioiodine therapy. The diffuse sclerosing variant of PTC has a higher incidence of gross extrathyroidal extension, cervical node involvement, and distant metastasis than classic PTC. The disease-free survival in patients with diffuse sclerosing PTC is shorter than in patients with classic PTC; however, overall mortality is similar in both.

What Morphologic Features Separate Neoplastic Follicular Lesions From Normal Thyroid Tissue and Nonneoplastic Hyperplastic Nodules?

Begin with the normal thyroid histology which shows numerous follicles that are the functional units of the thyroid (Figure 7). Thyroid function is regulated in individual follicles and active follicles often have endocytotic vesicles that are seen as unstained colloidal resorption droplets adjacent to the follicular epithelium. Follicular epithelium adheres to the basement membrane at the edge of the follicle as simple cuboidal or low columnar epithelium that surrounds the central colloid. Follicular epithelium is composed of 2 types of cells. Follicular cells

Figure 5. Follicular carcinoma showing a proliferation of follicular with scant colloid, a thick fibrous capsule, and widespread invasion of tumor into and through the fibrous capsule. Chromatin is dark and nuclei are round. A, ×40 scale bar 500 μm. B, ×400 scale bar 50 μm.
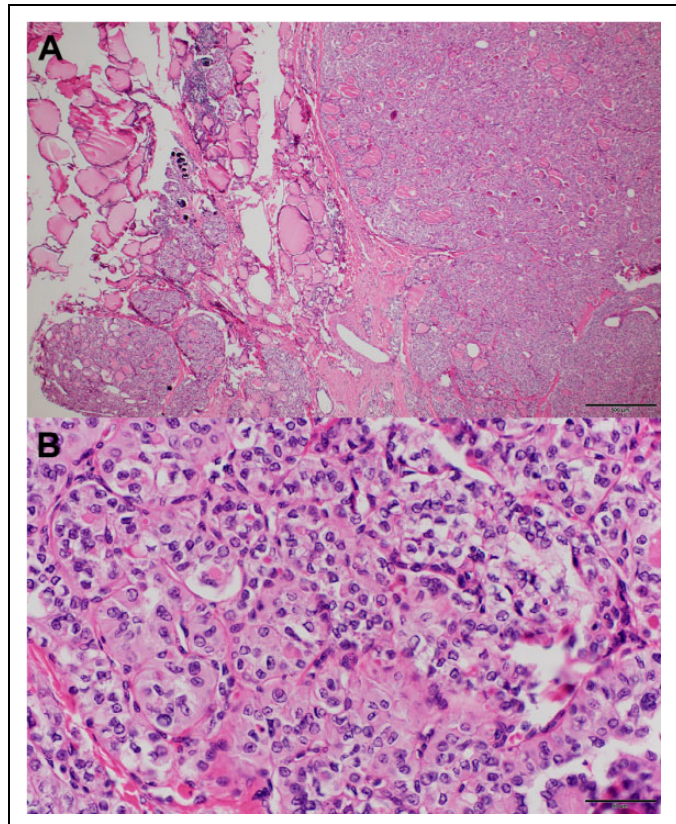
Figure 6. Papillary thyroid carcinoma, follicular variant with a follicular architecture and an infiltrative invasive growth pattern. Nuclei have pale chromatin, some nuclear grooves, and occasional small peripheral nucleoli. A, ×40 scale bar 500 μm. B, ×400 scale bar 50 μm.

(principal cells) display short microvilli on their apical surface where they release thyroglobulin and thyroid peroxidase to the colloid. Follicular cells endocytose iodinated thyroglobulin and release T4 and T3 from their basal surface where these hormones can enter blood. Parafollicular cells (C cells) are located between the follicular cells and the basement membrane where they secrete calcitonin. Circulation is regulated by fenestrated capillaries and blind-ended lymphatic capillaries in the connective tissue between follicles.

This relative uniformity of normal thyroid follicles contrasts with nonneoplastic (hyperplastic) nodules which show a similar follicular architecture with luminal colloid, but with variably enlarged follicles, some with abundant colloid, and overall show increased variability in overall size. Nonneoplastic (hyperplastic) nodules are usually multiple and nonencapsulated (Figure 7), but a large dominant adenomatoid hyperplastic nodule can clinically mimic a neoplasm.

The histology of follicular neoplasms (FA and FC) usually shows a predominance of small follicles with limited colloid, a microfollicular pattern (Figures 4 and 5), and a well-formed fibrous capsule surrounds the nodule, and this is one of the classic hallmark findings in follicular neoplasms distinguishing them from nonneoplastic nodules.

What Morphologic Features Separate Follicular Adenoma From Follicular Carcinoma?

Neoplastic nodules with a follicular architecture (FA and FC) are usually solitary, with a distinct fibrous capsule. In FA, the fibrous tumor capsule is usually relatively thin, and in FC usually thick. Both FA and FC are usually composed predominantly of small microfollicles with little colloid. Cytologic features (nuclear pleomorphism and anaplasia) are not reliable in distinguishing between hyperplastic nodules, FC, and FA. The defining pathologic feature for FC rather than FA is the presence of capsular invasion and/or vascular invasion which can only be identified in histologic sections, and this explains the inability of thyroid FNAB to distinguish FA and FC. The capsular and vascular invasion can be focal, and complete pathologic examination of the entire tumor capsule is essential to adequately exclude malignancy.

What Are the Molecular Changes That Are Characteristic of Follicular Adenoma, Follicular Carcinoma, and Papillary Thyroid Carcinoma?

Follicular adenomas are clonal neoplasms and various cytogenetic abnormalities have been found in about 50% of
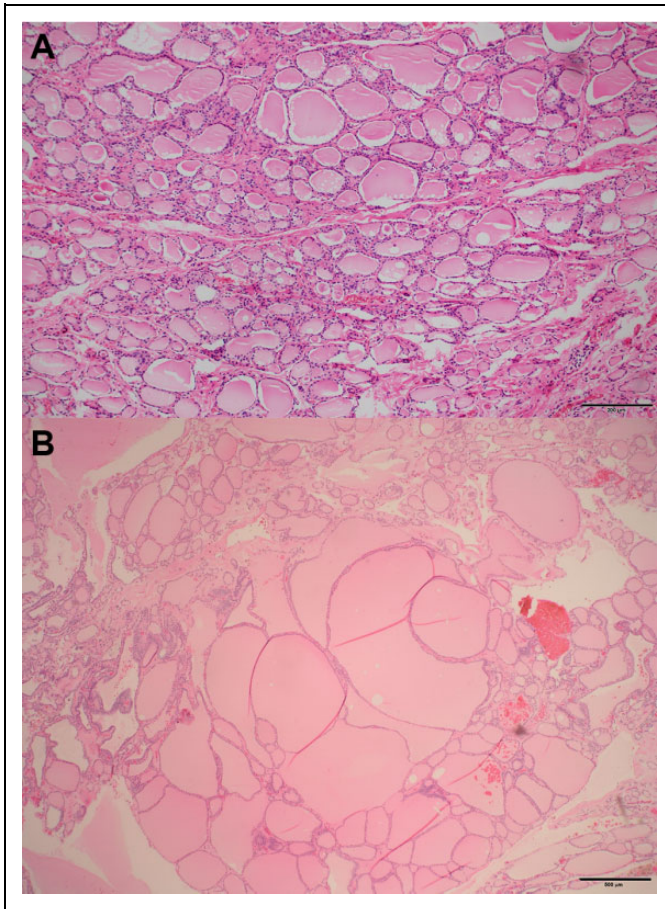
Figure 7. A, Normal thyroid gland histology with fairly uniform colloid-filled follicles, scale bar 200 μm. B, Multinodular thyroid hyperplasia with markedly variable-sized colloid filled follicles in expansive nodules without a fibrous capsule, scale bar 500 μm.

adenomas. Somatic *RAS* mutations are found in about 30% of FA. Papillary thyroid carcinoma may harbor gain-of-function mutations in *RET*, *NTRK1*, and BRAF. *RET/PTC* rearrangements and *BRAF* point mutations are not seen in follicular neoplasms (FA and FC). Follicular carcinomas are often associated with activated RAS or the PI-3K/AKT arm of the receptor tyrosine kinase pathway through gain-of-function mutations of *RAS* or *PIK3CA* or loss-of-function mutations in *PTEN*. Thus, PTC and FC have distinct molecular pathways of tumorigenesis.[3,4] Molecular diagnostics can be used on FNAB material to look for carcinoma-associated genetic changes when the morphology is ambiguous, and specific genetic changes are used to help identify nodules that require surgical intervention.[5]

What Are the Prognostic Differences Between Follicular Adenoma, Follicular Carcinoma, and Papillary Thyroid Carcinoma?

Follicular adenoma is a benign neoplasm, and surgical excision is curative with no metastasis and no recurrence when completely removed. In general, FA are not precursor lesions to FC,

although a subset of FA shares genetic abnormalities with FC; thus, it is possible that some FCs arise from a preexisting FA.

Follicular carcinoma accounts for 5% to 15% of primary thyroid cancers, shows capsular and/or vascular invasion on histology, and has metastatic potential. However, tumors with only focal capsular invasion (minimally invasive FC) have an excellent prognosis when vascular invasion is absent. These minimally invasive FCs have a 10-year survival in excess of 90%. The presence of even focal vascular invasion is associated with increased risk for hematogenous metastasis. Regional node involvement is uncommon in FC. In patients with widely invasive FC, metastasis is frequently noted at presentation, and nearly 50% die of disease within 10 years. The greater the degree of vascular invasion present histologically, the greater the increased risk of metastasis. Metastasis can be seen in bone, lung, brain, and liver most frequently, but other sites such as skin have been described.

What Clinical Features Suggest and Distinguish Neoplastic Nodules From Nonneoplastic Nodules, and Benign Neoplastic Nodules From Malignant Nodules?

Follicular adenoma, FC, and PTC can all have the common clinical presentation of an enlarging solitary thyroid nodule in a background of normal thyroid gland tissue. The prevalence of palpable solitary thyroid nodules ranges from 1% to 10%. The majority of solitary thyroid nodules are nonneoplastic and include dominant adenomatoid hyperplastic nodules, nodular thyroiditis, or cysts. Benign solitary neoplastic nodules (FA) greatly outnumber cancers and the ratio is about 10:1. Overall about 1% of solitary thyroid nodules are malignant, but still about 15 000 new thyroid cancers are found yearly in the United States. Ultrasound, as used in this case, is the preferred imaging modality for thyroid nodule characterization, and ultrasound-guided FNAB is the preferred tissue sampling technique to determine which nodules require surgical management. Fortunately, most thyroid cancers are relatively indolent with an overall 20-year survival of about 90%.[4,6]

Clinical features associate with and suggest neoplastic versus nonneoplastic solitary thyroid nodules, but definitive classification requires pathologic evaluation. Features favoring a neoplastic nodule include solitary, young patient age, male patient, cold nonfunctional nodule, and prior radiation exposure.[4] There are important clinical findings which increase the risk of malignancy in a nodule. These include prior head and neck radiation exposure, particularly in childhood, rapid growth and size increase, size over 4 cm, a nodule fixed to adjacent tissue, dysphagia, cervical adenopathy, age under 20 and over 70, and family history of multiple endocrine neoplasia or medullary thyroid carcinoma.[6]

Describe the Typical Treatment for Primary Thyroid Carcinoma

Treatment for PTC and FC typically is total thyroidectomy. Radioactive iodine is subsequently used to ablate residual and

metastatic disease, and since thyroid-stimulating hormone (TSH) can stimulate growth of FC, thyroid hormone is given to maintain a euthyroid state and suppress TSH levels. Serum thyroglobulin should be negative in a patient in remission, but is expected to increase with recurrence, and thus can be used for monitoring the patient clinically for recurrence.

There has been a recent increase in the incidence of PTC in the United States, due at least in part to the finding of small incidental nodules on imaging studies performed for reasons other than a clinically apparent neck/thyroid nodule.[7] Many of these are 1 cm or less and are classified as papillary microcarcinomas. Autopsy studies show a relatively high incidence of clinically occult papillary microcarcinomas, suggesting that aggressive surgical treatment is not indicated for such lesions unless there is clinical evidence of progression.[8]

Teaching Points

- Palpable neck masses include lesions of congenital, inflammatory/infectious, and neoplastic origins of which thyroid neoplasia is a common source.
- Thyroid gland ultrasound and ultrasound-guided FNAB are the usual clinical tools for characterizing thyroid nodules and providing a tissue diagnosis to identify nodules requiring surgery.
- Cytopathology is a useful diagnostic approach in a variety of settings to aid in the pathologic staging of various cancers.
- The 3 most common thyroid neoplasms are FA (benign), and FC and PTC (malignant).
- Clinical findings in thyroid nodules may suggest a benign or malignant nodule, but tissue diagnosis is required and FNAB is used to identify nodules requiring surgical excision.
- Papillary thyroid carcinoma spreads through lymphatics and often involves neck lymph nodes, while FC spreads by the hematogenous route with distant metastasis rather than neck lymph node involvement.
- Follicular adenoma and FC are thyroid tumors of the follicular epithelium showing a follicular architecture with a well-formed capsule and are distinguished by the absence (FA) or presence (FC) of capsular and/or vascular invasion and not by nuclear cytology.
- Papillary thyroid carcinoma is a malignant thyroid neoplasm characterized predominantly by characteristic nuclear features of oval nuclei with prominent nuclear grooves, pale chromatin, small peripheral nucleoli, and nuclear pseudoinclusions which classically has a papillary architecture, but a variant with follicular architecture exists.
- Benign and malignant thyroid nodules have distinct molecular profiles, and molecular testing can be of use in conjunction with FNAB in identifying thyroid nodules requiring surgery. *RET* and *BRAF* mutations are common in PTC, while *RAS* and *PI-3K/AKT* mutations are more typical of FC, while most benign nodules lack these mutations.

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References

1. Sira J, Zvoru G, Makura G. Differential diagnosis of cystic neck lesions. *Anal Oto Rhino Laryn*. 2011;120:409-413.
2. Amin MB, Edge S, Greene F, et al., eds. *AJCC Cancer Staging Manual*. 8th ed. Chicago, IL: Springer; 2017:873-890.
3. Lloyd RV, Osamura RY, Kloppel G, Rosi J. *WHO Classification of Tumours of Endocrine Organs*. 4th ed. Lyon, France: International Agency for Research on Cancer (IARC); 2017:69-95.
4. Maitra A. The endocrine system. In: Kumar V, Abbas A, Aster A, eds. *Robbins and Cotran Pathologic Basis of Disease*. 9th ed. Philadelphia, PA: Elsevier Sanders; 2015:1092-1099.
5. Onenerk AM, Pusztaszeri MP, Canberk S, Faquin WC. Triage of the indeterminate thyroid aspirate: what are the options for the practicing cytopathologist. *Cancer Cytopathol*. 2017;125:477-485.
6. Bomeli SR, LeBeau SO, Ferris RL. Evaluation of a thyroid nodule. *Otolaryngol Clin North Am*. 2010;43:229-238.
7. Brito JP, Morris JC, Montori VM. Thyroid cancer: zealous imaging has increased detection and treatment of low risk tumors. *BMJ*. 2013;347:f4706.
8. Fisher SB, Perrier ND. The incidental thyroid nodule. *CA Cancer J Clin*. 2018;68:97-105.