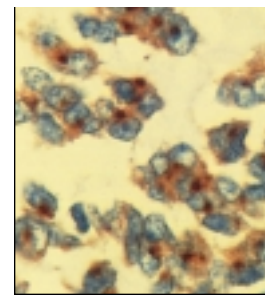


TUMORS OF THE THYROID GLAND: HISTOLOGIC AND CYTOLOGIC FEATURES — PART 2

Carlos A. Muro-Cacho, MD, PhD, and Ni Ni K. Ku, MD

From the Pathology Department at the H. Lee Moffitt Cancer Center & Research Institute at the University of South Florida, Tampa, Fla.
E-mail: murocacho@moffitt.usf.edu



This regular feature presents special issues in oncologic pathology.

Introduction

Tumors of parafollicular cells and nonepithelial tumors occur less frequently than tumors derived from follicular cells. This review summarizes the histologic and cytologic features of these neoplasms and the nonneoplastic diseases that often have to be included in the differential diagnosis of thyroid tumors. Also, the role of fine-needle aspiration biopsy and frozen section interpretation in the diagnosis of thyroid nodules are discussed.

ular basal lamina and from the colloid by extensions of the follicular-cell cytoplasm. C cells in diffuse hyperplasia exhibit intense immunoreactivity for calcitonin and are rich in granules ultrastructurally. The diagnosis of nodular C-cell hyperplasia should be made only when C cells completely obliterate the follicular space in a diffuse, bilateral, and multifocal manner. Foci of nodular C-cell hyperplasia can be difficult to distinguish from squamous metaplasia, solid cell nests, intrathyroidal thymic tissue, parathyroid nests, palpation thyroiditis, and tangential cuts of normal follicles.

C-Cell Hyperplasia

C-cell hyperplasia is an uncommon multifocal proliferation of C cells within the follicles of the thyroid gland.^{1,4} It has been recognized as a preneoplastic condition in multiple endocrine neoplasia (MEN) type 2A and 2B and is used histologically to distinguish sporadic and familial forms of medullary carcinoma. C-cell hyperplasia has also been reported in residual thyroid tissue after surgical resection of an apparently sporadic medullary carcinoma and occasionally in thyroid glands from patients with hyperparathyroidism, hypercalcemic states, hypergastrinemia, Hashimoto's thyroiditis, and follicular and papillary neoplasms. The diagnosis of diffuse (non-nodular) C-cell hyperplasia should be made when the process involves both lobes with at least 50 C cells per low-power field.^{5,7} C cells should be in an intrafollicular position separated from the interstitium by the follic-

Medullary Carcinoma

Medullary carcinoma (MC) is a rare neoplasm that arises from C or parafollicular cells and accounts for 5% to 10% of all thyroid malignancies.^{1,8,9} MC can occur sporadically (70% of cases) or in familial (autosomal dominant pattern) forms.^{5,10} Sporadic (nonfamilial) MC may be associated with Hashimoto's disease or chronic hypercalcemia, but it appears to be unrelated to irradiation. Familial MC occurs in association with tumors of the adrenal medulla and parathyroid gland, in the context of MEN 2A, or with neural proliferations, adrenal lesions or marfanoid habitus, in the context of MEN 2B. Depending on the peptide secreted and the association with other lesions, patients with MC may present with severe watery diarrhea, carcinoid and Cushing's syndromes, adrenal or parathyroid disease, hypertension, or cardiac arrhythmias.

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Sporadic MC is a tumor of middle-aged adults with a slight female predominance. It is usually unilateral and may present with cervical nodal metastases and, rarely, with distant metastases. The tumor has an indolent course with 5-year survival rates of 60% to 70% after surgery. Patients with MEN 2A are usually in the second decade and often have slow-growing, multicentric bilateral tumors. Patients with MEN 2B are slightly younger (average age = 15 years) and harbor aggressive neoplasms that metastasize early and have a poor prognosis. MC tumors vary in size from poorly demarcated minute foci at the junction of the upper and middle thirds of the thyroid lobes (areas in which C cells predominate) to tumors that replace the entire gland and mimic follicular, papillary, or undifferentiated carcinomas. The typical MC tumor is solid with a lobular, trabecular, insular, or sheet-like architecture and is

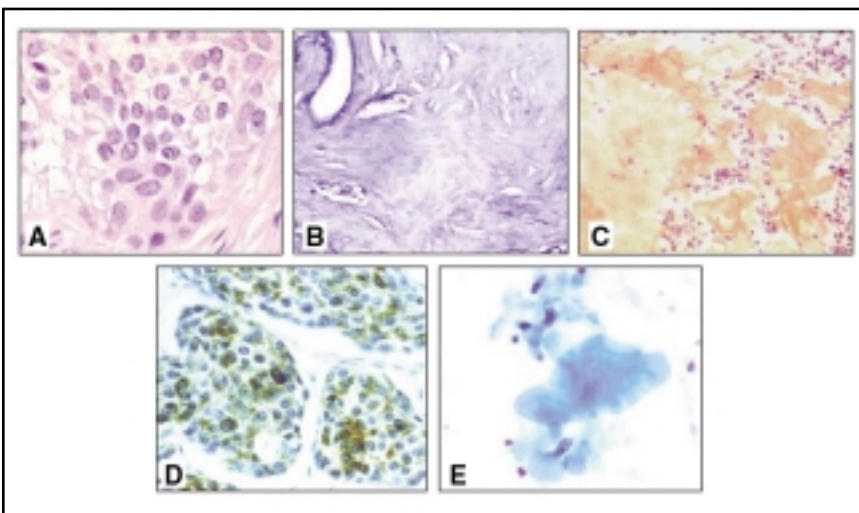
composed of a mixture of round, polygonal, or spindle-shaped cells (Fig 1A). Binucleated cells, giant cells, and cytoplasmic pseudoinclusions can be seen. The cytoplasm is eosinophilic-amphophilic and finely granular, but it may be clear or contain mucin. Necrosis, hemorrhage, and mitotic activity are uncommon, particularly in small tumors. Lymphatic and vascular invasion may be seen at the periphery of the tumor and in advanced cases in the contralateral lobe. The stroma contains collagen and, in 80% of the cases, amyloid deposits that are Congo red-positive and show green birefringence with polarized light (Figs 1B-C).

In familial MC, foci of C-cell hyperplasia are sometimes present away from the main tumor. By immunohistochemistry, MCs are typically positive for low-molecular-weight cytokeratin, carcinoembryonic antigen (CEA), calcitonin

(80% of cases; Fig 1D), neuron-specific enolase, synaptophysin, and chromogranin (chromogranin may in fact be a more specific marker than calcitonin). Ultrastructurally, calcitonin and other hormonal products are stored in two types of membrane-bound secretory granules. Type I granules (280 nm) are moderately electron-dense with finely granular contents closely applied to the membrane. Type II granules (130 nm) are more electron-dense, and their contents are separated from the membrane by a narrow electron-lucent space.

The probability of nodal metastases increases with the size of the primary tumor. Nodal metastases have been reported in 20% of patients with tumors less than 0.7 cm, in 30% of patients with tumors between 0.7 and 1.5 cm, and in 80% of patients with tumors greater than 1.5 cm. Sites of metastasis are central and lateral cervical nodes, lung, liver, bone, and adrenal glands. Survival correlates with age and sex of the patient and stage of the disease. Patients under 40 years old at the time of diagnosis have a significantly better prognosis than older patients, even when individuals with the familial form of the disease are excluded from analysis. In addition, women have a better prognosis than men.^{1,2}

Because many variants of MC have been described, MC may mimic a wide variety of benign and malignant primary thyroid neoplasms. MC contains follicular structures or entrapped thyroid follicles and must therefore be distinguished from follicular carcinomas.



Figs 1A-E. — Medullary carcinoma. (A) Homogeneous cellularity with minimal atypia and solid growth pattern. (B) Amyloid (Hematoxylin-eosin stain). (C) Amyloid (Congo red stain). (D) Calcitonin immunostain. (E) Rare oval-shaped cells and amyloid material (Papanicolaou stain).

In entrapped follicles and follicular carcinomas, both colloid and follicular cells are thyroglobulin-positive and calcitonin-negative. MC must also be distinguished from poorly differentiated or insular thyroid carcinomas. Insular carcinomas are characterized by solid islands containing small follicles, but the stroma is negative for amyloid and the tumor cells are thyroglobulin-positive and calcitonin-negative. MC spindle-cell and giant-cell types must be distinguished from undifferentiated carcinomas and sarcomas. MC with small-cell features and an oncocyctic or clear-cell appearance must be distinguished from small-cell carcinoma and metastatic renal-cell carcinoma.

Cytopathology of Medullary Carcinoma

Fine-needle aspirates are variably cellular depending on the amount of fibrosis. Amyloid appears as amorphous clumps of pale pink to violet Congo red positive material (Fig 1E). Tumor cells may be seen singly or in loosely cohesive groups with poorly defined cell borders. The cells are of variable morphology and appear as small, round, oval, cuboidal, polygonal, or spindle-shaped. The nuclei are round or elongated and always eccentrically located (plasmacytoid appearance) and the coarsely granular chromatin is described as "salt and pepper." Nuclear molding (neuroendocrine like features), inconspicuous nucleoli, bi- and multinucleation, indistinct delicate cytoplasmic borders with occasional fine and granular

cytoplasm and dendritic cell processes are common. The main diagnostic pitfalls are lymphoma, papillary carcinoma, and Hürthle cell carcinoma.^{5,6}

Primary Nonepithelial Tumors

Lymphoma

Primary thyroid lymphoma constitutes 8% of all thyroid malignancies.^{7,11,12} The term is reserved for those cases where the thyroid gland is the predominant or often exclusive site of involvement, and therefore it should not be used for secondary involvement by a systemic lymphoma or leukemia, which is found in 10% of autopsies. In approximately 80% of thyroid lymphomas, the residual nonneoplastic gland exhibits features of Hashimoto's or lymphocytic thyroiditis. This association is more frequent with lymphoma than with thyroid carcinoma. However, only a small percentage of patients with thyroiditis develop primary lymphoma of the thyroid. In fact, most primary thyroid lymphomas occur in middle-aged or elderly patients with a ratio of women-men ranging from 2:1 to 8:1. Patients present with a relatively rapid thyroid enlargement accompanied by hoarseness, dysphagia and/or dyspnea in approximately 25% of cases and cord paralysis in about 17%. In most cases, the tumor is an ill-defined, solid mass with a homogeneous, bulging, white surface lacking encapsulation. Most tumors are diffuse, large B-cell or immunoblastic non-Hodgkin's lymphomas. Poorly differentiated lym-

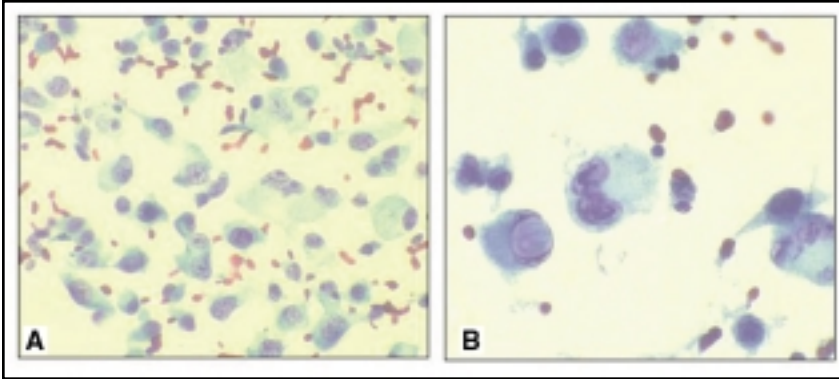
phocytic (small-cleaved) and intermediate types occur less frequently. Some authors consider these lymphomas neoplasms of mucosa-associated lymphoid tissue (MALT). Primary thyroid lymphomas will be of T-cell origin only exceptionally.

Hodgkin's Disease

It is exceptional for Hodgkin's disease to involve primarily the thyroid gland.. Most cases have been of the nodular sclerosis type, and some have involved the regional lymph nodes. Involvement of the thyroid in cases of systemic Hodgkin's disease is also rare.¹³

Cytopathology of Lymphoma

Cytologic specimens from malignant lymphomas are characterized by a monotonous population of discohesive atypical cells with large, irregular vesicular nuclei, prominent nucleoli, and scant cytoplasm (Figs 2A-B). The most important differential diagnosis is from Hashimoto's thyroiditis. In this condition, the lymphoid population is polymorphic and accompanied by plasma cells, macrophages, and oncocyctic cells. Hashimoto's thyroiditis and malignant lymphoma often coexist. Ancillary techniques such as immunohistochemistry, flow cytometry, and gene rearrangement studies can help to establish the definitive diagnosis. The main diagnostic pitfalls are chronic lymphocytic (Hashimoto's) thyroiditis, Hodgkin's lymphoma, and reactive lymphoid hyperplasia.



Figs 2A-B. — Cytologic features of metastatic melanoma to the thyroid gland. Cellular aspirate with discohesive abnormal cells exhibiting pleomorphic enlarged nuclei, binucleation, macronucleoli, intranuclear pseudoinclusions and scant to abundant cytoplasm (Papanicolaou stain).

Plasmacytoma

Involvement of the thyroid gland by a plasma-cell malignancy can be seen as an expression of widespread myeloma or as the only manifestation of the disease (plasmacytoma). Plasmacytoma should be distinguished from lymphoma exhibiting plasmacytoid features (ie, immunoblastic lymphoma), some forms of small lymphocytic lymphoma, and “pleomorphic immunocytoma.” In true plasmacytoma, all of the tumor cells have the appearance of plasma cells exhibiting various degrees of immaturity or atypia, whereas in lymphomas, the plasmacytoid elements alternate with cells of lymphoid type. Primary plasmacytoma of the thyroid is often accompanied by evidence of autoimmune thyroiditis in the remainder of the gland.¹⁴

Sarcoma

Sarcomas are malignant tumors of mesenchymal derivation arising within the thyroid

gland. Undifferentiated (anaplastic) carcinoma can be impossible to distinguish from sarcoma. Sarcoma-like tumors of the thyroid should be regarded as undifferentiated thyroid carcinomas until proven otherwise. The issue is of no practical significance since sarcoma’s natural history and response to therapy do not differ significantly from those of undifferentiated carcinoma. The exception is angiosarcoma, a malignant tumor exhibiting endothelial cell differentiation (malignant hemangioendothelioma).^{8,15} The neoplastic cells express vascular markers (factor VIII, CD31, CD34, and ulex europaeus).

Secondary/Metastatic Tumors

The thyroid gland may be invaded by carcinomas of the pharynx, larynx, trachea, and esophagus, or by metastatic lesions in adjacent cervical lymph nodes. In view of the rarity of primary squamous-cell carcinoma of

the thyroid, the possibility of a metastasis should be considered whenever such a tumor type is present in a thyroid biopsy, particularly if the tumor is well to moderately well differentiated. Metastases to the thyroid from melanoma and carcinomas (lung, gastrointestinal tract, head and neck region, breast, and kidney) occur in 9.5% of autopsies.⁹

Cytopathology of Secondary/Metastatic Tumors

Metastatic Melanoma

Aspirates (Fig 2) are hypercellular with single, discohesive cells that have enlarged, eccentrically placed nuclei and frequent binucleation or multinucleation, prominent nucleoli, intranuclear pseudoinclusions, and moderately abundant cytoplasm with or without intracytoplasmic melanin pigment. Unusual cytologic features and previous history of melanoma do not help in reaching the diagnosis.

Metastatic Sarcoma

Aspirates may be hypocellular to cellular. The cytologic features reflect the histology of sarcomas ranging from malignant spindle cells in syncytial arrangements (malignant fibrous histiocytoma, fibrosarcoma, leiomyosarcoma) to lipoblasts of varying maturation in liposarcoma. The background may contain metachromatic myxoid or chondroid matrix material.

Metastatic Squamous-Cell Carcinoma

Metastatic squamous-cell carcinoma contains aspirates that are cellular with malignant squamous cells singly or in syncytial arrangements with enlarged nuclei, prominent nucleoli, and cytoplasm with squamoid or keratinizing features.

Tumor-like Conditions

Nodular Hyperplasia

Nodular, multinodular, adenomatous hyperplasia (or adenomatoid goiter) is a common thyroid disease. Due to low iodine content, the endemic form is the result of an increase in thyroid-stimulating hormone secretion. The gland initially responds with hyperplastic (tall) follicular epithelium and scanty colloid production (parenchymatous goiter). Later, however, the gland becomes atrophic and stores abundant colloid (colloid goiter). The sporadic form is the most common in the United States. The incidence in the general adult population is 3% to 5%; in autopsy series, the incidence is 50%. Some cases are considered the nodular forms of lymphocytic or Hashimoto's thyroiditis. Clinically, most patients are euthyroid and present with a multinodular gland that may cause tracheal obstruction. Hyperfunctional cases are called *toxic nodular hyperplasia*. The thyroid capsule is intact, and on cross-section, multiple partially encapsulated nodules are seen. Some are composed of dilated follicles lined by

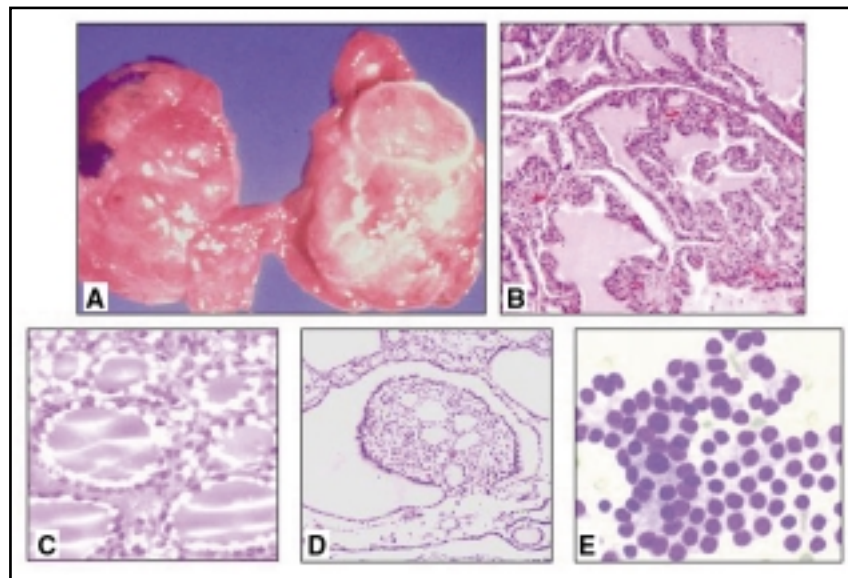
flattened epithelium, others are extremely cellular, and still others have oncocytes or clear cells (Figs 3A-C). Some of the dilated follicles have small, active follicles at one pole called *Sanderson's polsters* (Fig 3D). The rupture of follicles may provoke a granulomatous reaction to the colloid. Fresh and old hemorrhage, fibrosis, calcification, and osseous metaplasia are common. Nodular hyperplasia can simulate malignancy due to the presence of hypercellularity, vesicular (ground-glass-like) nuclei, papillae, and parasitic nodules.

Aspirates are hypocellular, and cytologic features reflect the stages of histologic evolution. Often present is a mixture of colloid and follicular cells arranged in macrofollicles or microfollicles or sheets with small round to oval

nuclei with regular nuclear outline and finely granular chromatin. Also present are naked nuclei of follicular cells and histiocytes with and without hemosiderin. Squamous metaplasia and hemosiderin-laden macrophages can be seen. The amount and quality of colloid vary, with some nodules being very cellular and containing minimal colloid. Oncocytic change can be confused with oncocytic tumors (Fig 3E). The main diagnostic pitfalls are follicular neoplasms and colloid cyst or goiter.¹ Cells with small nuclei and abundant cytoplasm are arranged in sheets with a honeycomb pattern.

Diffuse Hyperplasia (Graves' Disease)

The diffusely hyperplastic gland may simulate malignancy



Figs 3A-E. — Nodular hyperplasia. (A) Gross appearance of multinodular gland. (B) Hyperplastic thyroid epithelium. (C) Resorption of colloid in hyperplasia. (D) Sanderson's polster. (E) Cytologic features. Follicular epithelial cells with uniform small nuclei in monolayer-honeycomb and follicular patterns (Diff-Quik stain).

due to the presence of well-developed papillary formations, large vesicular nuclei in the follicular epithelium and occasional extension of the hyperplastic process into the skeletal muscle of the neck. The cytologic appearance varies with degree of activation.

Dyshormonogenetic Goiter

Dyshormonogenetic goiter is a genetic hyperplasia resulting from enzymatic defects in the synthesis of thyroid hormones and secondary hypersecretion of thyroid-stimulating hormone. The gland is hypercellular, and nuclear atypia can be prominent.

Hashimoto's Thyroiditis

Hashimoto's disease presents with a combination of epithelial damage and proliferation, prominent interstitial polymorphous inflammatory infiltrate with germinal center formation (Fig 4A), fibrotic bands, and frequent "oxyphilic" change in follicular cells. Active phases are associated with multinodularity and enlargement of the gland and later phases with atrophy and fibrosis.¹ Diffuse (Hashitoxicosis), nodular (nodular Hashimoto's thyroiditis), and fibrous variants should be distinguished from primary and metastatic squamous-cell carcinoma and from sclerosing mucoepidermoid carcinoma with eosinophilia.

Aspirates are usually cellular with numerous Hürthle cells singly or in discohesive clusters, forming microfollicles or macro-

follicles in a background rich in lymphocytes, plasma cells, and scant colloid (Figs 4B-D). A background of atypical lymphocytes often justifies the collection of nonfixed material for flow cytometric studies. The main diagnostic pitfalls are malignant lymphoma, Hürthle cell neoplasms and nodular hyperplasia with Hürthle cell metaplasia.

Granulomatous (de Quervain) Thyroiditis

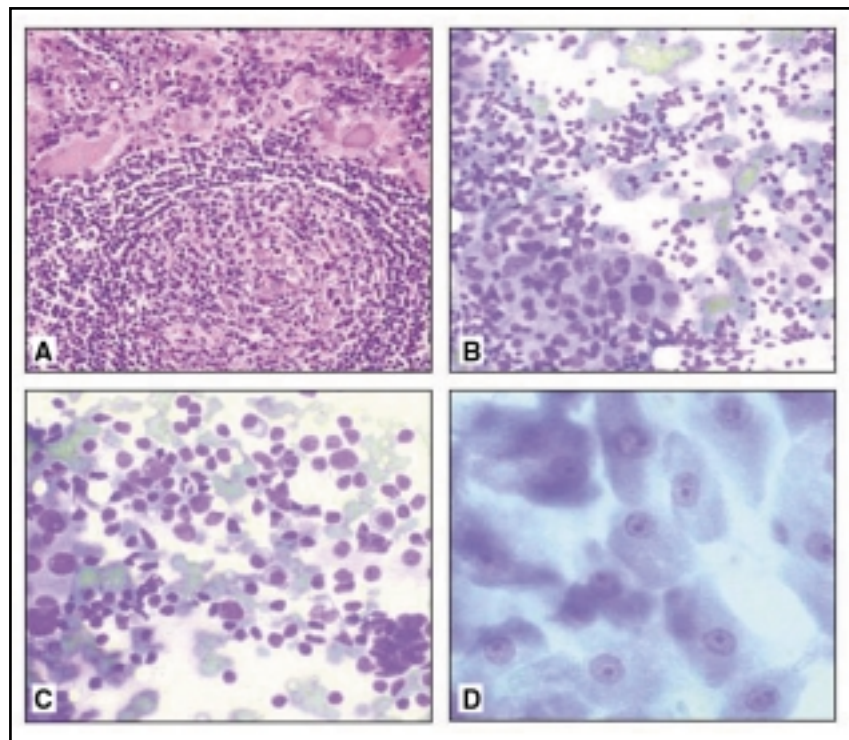
Granulomatous thyroiditis can simulate a malignancy clinically and grossly due to ill-defined nature of the margins (Figs 5A-B).

Fibrosing (Riedel) Thyroiditis

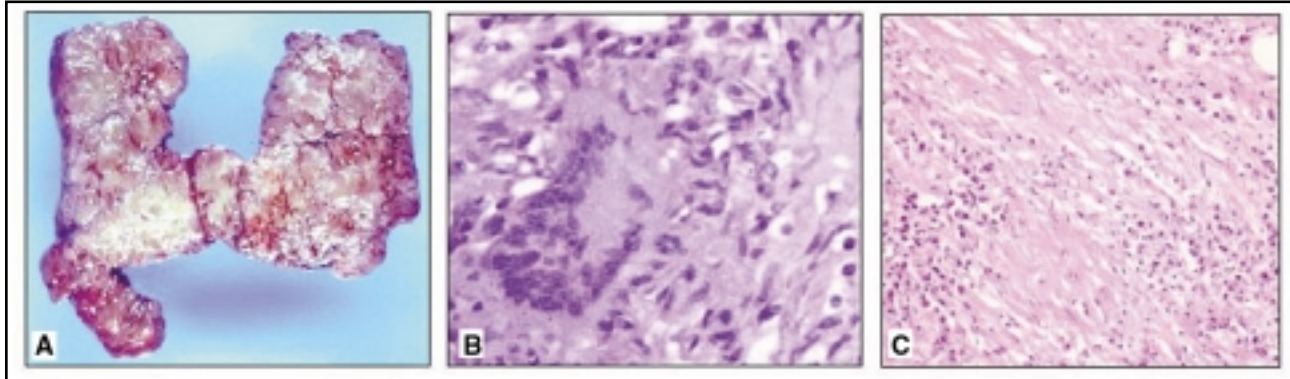
The fibrous process extends outside the thyroid into the surrounding soft tissues mimicking malignancy. Microscopically, the abundant collagen and prominent lymphoplasmacytic infiltrate (Fig 5C), and the lack of atypia should facilitate the distinction from spindle-cell anaplastic carcinoma, desmoplasia in papillary carcinoma, and lymphoma with sclerosis.

Amyloid Goiter

In most cases, the disease is accompanied by amyloid deposition



Figs 4A-D. — Hashimoto's thyroiditis. (A) Germinal center. (B, C and D). Cytologic features. (B) Hürthle cells singly and in clusters in a background of polymorphic lymphocytic population (Diff-Quik stain). (C) Prominent lymphocytes and plasma cells (Diff-Quik stain). (D) Reactive Hürthle cells in loose aggregate (Papanicolaou stain).



Figs 5A-C. — Granulomatous thyroiditis. (A) Gross appearance with multinodularity and fibrosis. (B) Multinucleated giant cell. (C) Fibrosis.

in other organs. The amyloid deposits may be unilateral or bilateral and are often associated with a foreign-body-type giant-cell reaction and adipose tissue. The differential diagnosis includes MC, the amyloidosis of multiple myeloma, and hyalinizing trabecular adenoma.

Thyroid Nodules

Approximately 4% of Americans between 30 and 60 years of age have one or more palpable thyroid nodules (one in 12 to 15 women and one in 40 to 50 men).^{16,17} However, only approximately 15,600 new thyroid cancer cases are reported annually (1.1% of the total number of new cancer cases of all sites), accounting for 1,200 deaths (0.2% of the total number of deaths related to cancer).¹⁸ Thus, most of these nodules are benign, and clinicians should be as selective as possible in recommending surgical removal.

Several factors should be considered when evaluating a nodule, including age, sex, geographic location, family history, characteristics

and rate of growth of the nodule, and presence of ipsilateral adenopathy (Table).

Fine-Needle Aspiration Biopsy

Fine-needle aspiration biopsy (FNAB) is quick, inexpensive, and diagnostically accurate in experienced hands.^{16,17,19,21} Its accuracy can be further improved by ultrasound guidance and is considered the test of choice in the initial eval-

uation of any thyroid nodule. The most important aspect of FNAB interpretation is obtaining a high-quality sample; most mistakes occur when interpretation is attempted in a poor-quality sample. The patient is placed in a supine position with the head slightly elevated. Generally, a 22½- to 25-gauge needle is used. Minimal or no suction is applied to avoid aspirating excessive blood that may complicate interpretation. Tumor seeding or implantation has not

Factors in Thyroid Nodule Evaluation

Age	The incidence of malignancy is higher in children and the elderly.
Sex	The incidence of malignancy is higher in men.
Geographic location	Dietary iodine deficiency promotes the onset of thyroid cancer.
Family history	A strong family history (unrelated to dietary iodine deficiency) suggests the diagnosis of either dyshormonogenetic goiter or MC.
Rate of growth	Most adenomas and well-differentiated follicular or papillary carcinomas are slow growing. Rapid enlargement of a preexisting nodule may be related to the emergence of an undifferentiated malignant component or to spontaneous hemorrhage.
Characteristics	Solitary nodules are more likely to be malignant than multiple ones. However, one third of clinically solitary nodules are multiple on scan or after pathologic examination. A malignancy should be suspected if the nodule is hard, if there are irregular nodules in a multinodular gland, if the gland is fixed when swallowing, or if there is vocal cord paralysis.
Ipsilateral adenopathy	In the absence of infection, ipsilateral adenopathy is the strongest clinical indicator of malignancy.

been reported with thyroid tumors. For optimal results, two or three needle passes are recommended, and smears stained with both Papanicolaou and Diff-Quik should be prepared. The cytopathologist must be familiar with potential limitations and pitfalls and must use strict criteria for specimen adequacy. For proper smear interpretation of solid lesions, at least 6 well-preserved cellular clusters with a minimum of at least 10 cells in each cluster are needed. For cystic lesions, clinical judgment must be made before rendering a benign diagnosis. FNAB may result in transient elevation of thyroglobulin serum levels, partial or complete infarct of the tumor (particularly in oncocytic lesions), papillary hyperplastic changes, hemorrhage, and thrombosis. These changes can be misinterpreted as papillary carcinoma or angiosarcoma. At our center, diagnostic categories include *negative*, *atypical*, *suspicious*, and *diagnostic for malignancy*. Clinical correlation and possibly other studies are recommended for patients in the atypical and suspicious categories. The diagnostic accuracy of thyroid FNAB is generally reported in the range of 70% to 90%, but it is highly dependent on the aspirator and the interpreter. Generally, accepted false-negative rates and false-positive rates are 1% to 8% and 1% to 2%, respectively.

Although FNAB is sufficiently sensitive in the diagnosis of thyroiditis and carcinomas such as papillary, medullary, poorly differentiated, and anaplastic, it has a limited value in the distinction of benign

from malignant follicular lesions due to overlapping cytologic criteria. Ancillary techniques such as quantitative image analysis, DNA ploidy, immunohistochemistry for several markers, and quantitation of nucleolar-organizing regions have shown variable results.

Frozen Section Examination

The role of the frozen section in the management of thyroid nodules has greatly diminished after the widespread use of FNAB. It remains a subject of debate, and indications for its use should be established for each institution. Lesions that are usually identifiable by frozen section are widely invasive follicular carcinoma, poorly differentiated (insular) carcinoma, undifferentiated (anaplastic) carcinoma, MC, thyroiditis, and nodular hyperplasia (adenomatoid goiter). If typical papillae are identified, the diagnosis of papillary carcinoma can be made despite the fact that nuclear clearing is not as evident in frozen section analysis as it is cytologic examinations. Nuclear grooves, intranuclear pseudoinclusions, and nuclear grooves are readily identified in frozen sections. The most common diagnostic problem is the differential diagnosis of a single encapsulated nodule with follicular pattern. In this case, the differential diagnosis includes dominant hyperplastic nodule, follicular adenoma, minimally invasive follicular carcinoma, and encapsulated follicular variant of papillary carcinoma. The difficulty is due to the focal nature of capsular and vascular invasion in minimally invasive follicular carcinoma

as well as the absence of recognizable ground-glass nuclei on frozen tissue. In these circumstances, it is justified to defer diagnosis until permanent sections are examined. Several authors report similar sensitivity and specificity for FNAB and frozen section examination when used independently.^{17,22-28} It is generally agreed that frozen section analysis adds little to the intraoperative decision process if a definitive diagnosis of malignancy has been issued by preoperative FNAB. Less definitive interpretations, however, decrease the sensitivity, specificity, and accuracy of the FNAB diagnosis. On the other hand, a diagnosis of "follicular neoplasm" by FNAB is unlikely to be changed by frozen section examination, and many "deferrals to permanent" occur at the time of frozen section examination in follicular tumors. For these reasons, some authors have concluded that routine use of frozen sections is unnecessary and that adequate preoperative FNAB diagnosis and sound clinical judgment at the time of surgery can adequately guide the extent of surgical resection. In fact, clinical management is influenced in a low number of cases (between 3% and 5%). In some cases, frozen sections can actually mislead the surgeon. On the other hand, frozen sections should be considered whenever the FNAB diagnosis is suspicious for malignancy.²⁹ In 54% of these cases, a cancer is finally demonstrated by histologic evaluation. Although FNAB is a reliable first diagnostic step, a negative FNAB should never exclude malignancy if there is strong clinical suspicion. In general, when strict histologic and cyto-

logic criteria are applied, the combined use of both methods decreases the false-positive and false-negative values of each method used individually. Also, intraoperative evaluation of the tissue allows gross examination and intraoperative cytopathologic assessment by touch preparations, smears, or scrapings. This cytologic analysis at the time of frozen section together with recent modifications of the technique enhances overall diagnostic accuracy, particularly the recognition of papillary carcinomas. If malignancy is strongly suspected based on the combination of these methodologies, definitive surgery can be confidently planned since final histologic analysis will reveal malignancy in 90% of these cases. In contrast, if intraoperative evaluation is not diagnostic of malignancy, a conservative lobectomy-isthmusectomy is recommended because in 71% of these cases, final histologic evaluation will reveal a benign lesion.

References

- Rosai J, Carcangiu ML, Delellis RA. Tumors of the thyroid gland. In: *Atlas of Tumor Pathology*. 3rd series. Fasc 5. Washington, DC: Armed Forces Institute of Pathology; Bethesda, Md: Under the auspices of Universities Associated for Research and Education in Pathology; 1992.
- Teitelbaum SL, Moore KE, Shieber W. Parafollicular cells in the normal human thyroid. *Nature*. 1971;230:334-345.
- Hedinger CE. Histological typing of thyroid tumours. In: Hedinger CE, Williams Ed, Sobin LH, eds. *International Histological Classification of Tumours*. 2nd ed. Berlin, NY: Springer-Verlag; 1988.
- Lips CJ, Leo JR, Berends MJ, et al. Thyroid C-cell hyperplasia and micronodules in close relatives of MEN-2A patients: pitfalls in early diagnosis and reevaluation of criteria for surgery. *Henry Ford Hosp Med J*. 1987;35:133-138.
- Green I, Ali SZ, Allen EA, et al. A spectrum of cytomorphologic variations in medullary thyroid carcinoma. Fine-needle aspiration findings in 19 cases. *Cancer*. 1997;81:40-44.
- Frale WJ, Frable MA. Fine-needle aspiration biopsy of the thyroid. Histopathologic and clinical correlations. In: Fenoglio CM, Wolff M, eds. *Progress in Surgical Pathology*. New York, NY: Masson Pub; 1980:105-118.
- Aozasa K, Inoue A, Tajima K, et al. Malignant lymphomas of the thyroid gland. Analysis of 79 patients with emphasis on histologic prognostic factors. *Cancer*. 1986; 58:100-104.
- Hedinger CE. Sarcomas of the thyroid gland. In: Hedinger CE, ed. *Thyroid Cancer*. Berlin: Springer-Verlag; 1969:47-52. UICC monograph series; Vol 12.
- McCabe DP, Farrar WB, Petkov TM, et al. Clinical and pathologic correlations in disease metastatic to the thyroid gland. *Am J Surg*. 1985;150:519-523.
- LiVolsi VA. Surgical pathology of the thyroid. In: Bennington JL ed. *Major Problems in Pathology*. Vol 22. Philadelphia, Pa: Saunders; 1990.
- Hyjek E, Isaacson PG. Primary B cell lymphoma of the thyroid and its relationship to Hashimoto's thyroiditis. *Hum Pathol*. 1988;19:1315-1326.
- Mizukami Y, Matsubara F, Hashimoto T, et al. Primary T-cell lymphoma of the thyroid. *Acta Pathol Jpn*. 1987;37:1987-1995.
- Feigin GA, Buss DH, Paschal B, et al. Hodgkin's disease manifested as a thyroid nodule. *Hum Pathol*. 1982;13:774-776.
- Shimaoka K, Gailani S, Tsukada Y, et al. Plasma cell neoplasm involving the thyroid. *Cancer*. 1978;41:1140-1146.
- Chan YF, Ma L, Boey JH, et al. Angiosarcoma of the thyroid. An immunohistochemical and ultrastructural study of a case in a Chinese patient. *Cancer*. 1986; 57:2381-2388.
- Sidawy MK, Del Vecchio DM, Knoll SM. Fine-needle aspiration of thyroid nodules: correlation between cytology and histology and evaluation of discrepant cases. *Cancer*. 1997;81:253-259.
- Boyd LA, Earnhardt RC, Dunn JT, et al. Preoperative evaluation and predictive value of fine-needle aspiration and frozen section of thyroid nodules. *J Am Coll Surg*. 1998;187:494-502.
- Parker SL, Tong T, Bolden S, et al. Cancer statistics, 1996. *CA Cancer J Clin*. 1996;46:5-27.
- Keller MP, Crabbe MM, Norwood SH. Accuracy and significance of fine-needle aspiration and frozen section in determining the extent of thyroid resection. *Surgery*. 1987;101:632-635.
- Layfield LJ, Mohrmann RL, Kopald KH, et al. Use of aspiration cytology and frozen section examination for management of benign and malignant thyroid nodules. *Cancer*. 1991;68:130-134.
- Bugis SP, Young JE, Archibald SD, et al. Diagnostic accuracy of fine-needle aspiration biopsy versus frozen section in solitary thyroid nodules. *Am J Surg*. 1986; 152:411-416.
- Taneri F, Poyraz A, Tekin E, et al. Accuracy and significance of fine-needle aspiration cytology and frozen section in thyroid surgery. *Endocr Regul*. 1998; 32:187-191.
- Chen H, Zeiger MA, Clark DP, et al. Papillary carcinoma of the thyroid: can operative management be based solely on fine-needle aspiration? *J Am Coll Surg*. 1997;184:605-610.
- Shemen LJ, Chess Q. Fine-needle aspiration biopsy diagnosis of follicular variant of papillary thyroid cancer: therapeutic implications. *Otolaryngol Head Neck Surg*. 1998;119:600-602.
- Paphavasit A, Thompson GB, Hay ID, et al. Follicular and Hürthle cell thyroid neoplasms. Is frozen-section evaluation worthwhile? *Arch Surg*. 1997;132:674-678.
- Lin HS, Komisar A, Opher E, et al. Surgical management of thyroid masses: assessing the need for frozen section evaluation. *Laryngoscope*. 1999;109:868-873.
- Boyd LA, Earnhardt RC, Dunn JT, et al. Preoperative evaluation and predictive value of fine-needle aspiration and frozen section of thyroid nodules. *J Am Coll Surg*. 1998;187:494-502.
- Tworek JA, Giordano TJ, Michael CW. Comparison of intraoperative cytology with frozen sections in the diagnosis of thyroid lesions. *Am J Clin Pathol*. 1998;110:456-461.
- Mulcahy MM, Cohen JI, Anderson PE, et al. Relative accuracy of fine-needle aspiration and frozen section in the diagnosis of well-differentiated thyroid cancer. *Laryngoscope*. 1998;108(4 Pt 1):494-496.