

*This regular feature
presents special issues
in oncologic pathology.*

TUMORS OF THE THYROID GLAND: HISTOLOGIC AND CYTOLOGIC FEATURES — PART 1

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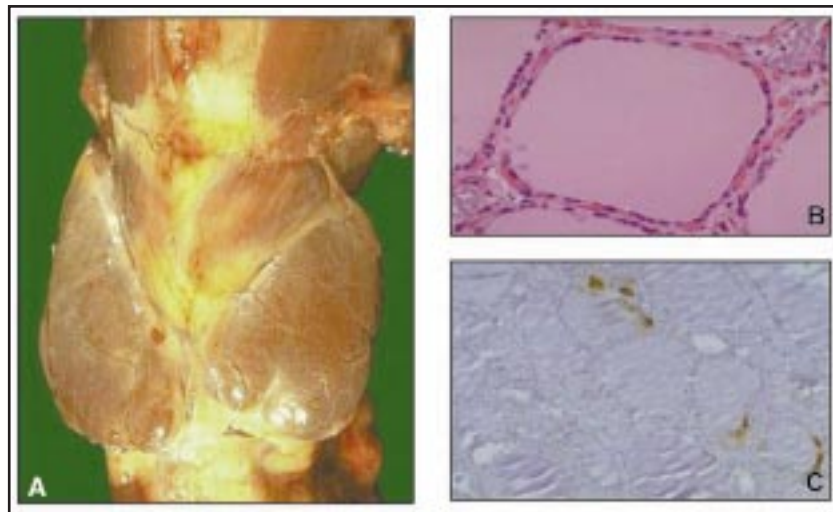
Introduction

Every year, 18,000 new thyroid cancer cases are reported in the United States, representing 1.2% of the total number of new cancer cases of all sites. Thyroid cancer accounts for 1,200 deaths, or 0.2% of the total number of deaths related to cancer.¹ Over the last two decades, there has been important progress in our understanding of tumors of the thyroid gland, from both histopathologic and etiopathogenetic points of view. In the first part of this review, we summarize the histologic and cytologic features of benign and malignant tumors of the thyroid gland that derive from follicular cells.

Normal Histology of the Thyroid Gland

The thyroid gland, located in the anterior aspect of the trachea

below the cricoid cartilage (Fig 1A), is composed of two lobes joined by an isthmus from which, in a significant number of normal individuals, the “pyramidal lobe” extends upward. The adult gland varies in size and appearance according to functional activity, gender, hormonal status, and iodine intake. On average, the adult thyroid gland weighs 15 to 25 g, with each lobe measuring 4.0 × 2.0 × 4.0 cm (the right lobe is usually larger) and the isthmus measuring 2.0 × 2.0 × 0.6 cm.² The parathyroid glands are found posteriorly. Blood is supplied by the right and left superior thyroid arteries (branches of the external carotid artery) and the right and left inferior thyroid arteries (branches of the thyrocervical trunk). Veins drain into the internal jugular, brachycephalic, and anterior jugular veins. A rich intraglandular lymphatic network establishes numerous communications within the gland and con-



Figs 1A-C. — (A) Normal thyroid gland. (B) Normal thyroid follicles. (C) Parafollicular cells. Calcitonin immunostain.

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nects the lobes through the isthmus. Lymphatics drain into subcapsular channels and from there into pericapsular, internal jugular, pretracheal, paratracheal, prelaryngeal, retropharyngeal, and retroesophageal lymph nodes. A fibrous capsule surrounds the gland and connects with intrathyroidal fibrous septa to form lobules that average 200 nm in size and contain 20 to 40 follicles supplied by a single artery (Fig 1B).³ Follicles are round or oval sacs filled with colloid and lined by a monolayer of low-cuboidal follicular cells surrounded by a basement membrane. The other epithelial cell type found in the thyroid gland is the C cell (or parafollicular cell) that has granules containing calcitonin (Fig 1C). In the glands of normal adults, C cells are found predominantly in the middle to upper third regions of both lobes, occasionally in clusters of 50 or more cells.⁴

Embryologically, the thyroid anlage begins as a bilobate vesicular structure at the foramen cecum of the tongue and descends as a component of the thyroglossal duct to reach its definitive position in the anterior neck. After involution of the thyroglossal duct, the thyroid anlage expands laterally, forming the thyroid lobes, and thyroglobulin secretion begins. Microscopic cords and plates of follicular cells appear at the 9th week, follicular lumina at the 10th week, and colloid secretion at the 12th week. The gland is well developed by the 14th week. C cells, probably derived from the neural crest, migrate to the ultimobranchial bodies before their incorporation into the thyroid.⁵

Normal Cytology of the Thyroid Gland

Normal follicular cells in fine-needle aspiration biopsies (FNABs) are typically arranged in follicles and/or monolayered sheets with a honeycomb pattern, well-defined borders, and polarized nuclei. Minute tissue fragments and naked nuclei resembling lymphocytes are not uncommon, and colloid may be seen in various amounts.^{6,9}

Thyroid Tissue in Abnormal Locations

Abnormalities in migration along the pathway of the thyroglossal duct can result in ectopic thyroid tissue anywhere between the base of the tongue (lingual and sublingual thyroid) and the mediastinum.¹⁰ Thyroid tissue also can be found in thyroglossal duct cysts where it may undergo malignant transformation. Other sites where

ectopic thyroid tissue has been reported include the larynx, trachea, aortic arch, heart, pericardium, esophagus, diaphragm, gallbladder, common bile duct, retroperitoneum, vagina, sella turcica, inguinal region, and ovarian teratomas (struma ovarii). Mechanical implantation due to surgery or trauma has also been reported. Parasitic nodules can result from nodular enlargement of thyroid tissue outside the capsule. In the context of Hashimoto's disease, these nodules may mimic a lymph node metastasis. A particularly controversial issue is the presence of thyroid tissue within lymph nodes. A diagnosis of benign thyroid inclusion is favored when few unremarkable follicles are found in a subcapsular location. A diagnosis of metastasis is favored if the thyroid tissue shows features of papillary carcinoma (PC) or psammoma bodies, if it replaces one third or more of the node, or if several nodes are affected.^{2,10}

Classification of Primary Epithelial Tumors of the Thyroid Gland^{2,20,28}

	Malignant	Benign
Follicular Cell	Differentiated Follicular carcinoma (FC) - Minimally invasive - Widely invasive Papillary carcinoma (PC) - Conventional - Variants Poorly differentiated - Insular carcinoma (IC) - Other Undifferentiated (anaplastic)	Adenoma - Conventional - Variants
Oncocytic	Oncocytic adenoma Oncocytic carcinoma	
C Cell	Medullary carcinoma (MC)	

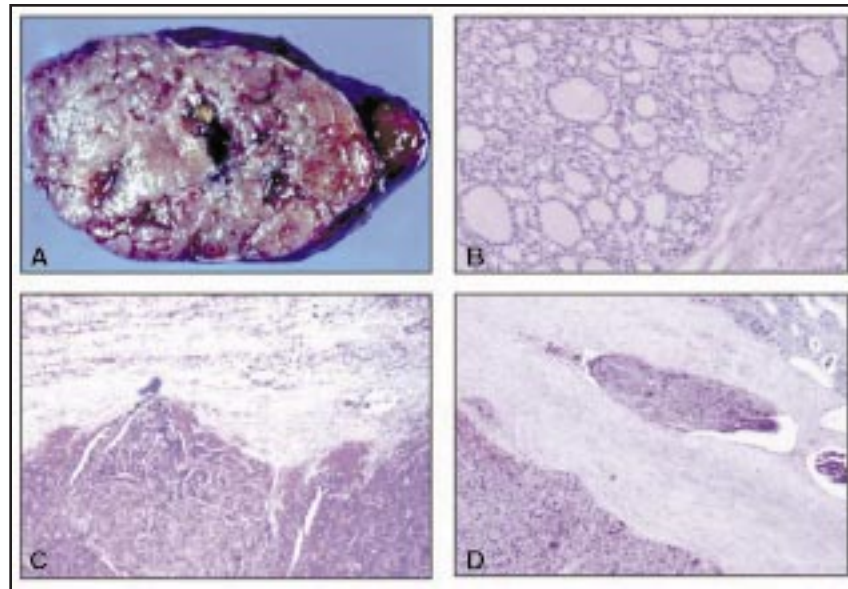
Primary Epithelial Thyroid Tumors

The thyroid gland contains only two major types of epithelial cells, the follicular cell and the parafollicular or C cell.^{2,11} Epithelial tumors are, therefore, best divided into those that exhibit follicular cell differentiation and those that exhibit C-cell differentiation (Table). Rare tumors showing dual differentiation have also been reported. Medullary carcinoma and its variants comprise the only major type of neoplasm showing C-cell differentiation. However, follicular neoplasms are divided into benign and malignant tumors. Benign tumors are designated as follicular adenomas, while their malignant counterparts are divided into two major categories, follicular and papillary. Tumors that show no obvious differentiation are classified as undifferentiated or anaplastic. From a prognostic point of view, the recognition of a tumor as poorly differentiated or anaplastic is more important than its recognition as follicular or papillary. A variety of histopathologic appearances (oncocytic, clear cell, squamous, and mucinous) can also be seen in tumors of both follicular and parafollicular origin.²

Tumors With Follicular Cell Differentiation

Follicular Adenoma

Follicular adenomas are found incidentally in 3% of autopsies. While they usually occur in otherwise normal glands, they can be seen in association with thyroiditis,



Figs 2A-D. — (A) Follicular adenoma with variegated gross appearance. (B) Follicular adenoma. The periphery of the tumor is surrounded by a fibrous capsule. (C) Follicular adenoma with indentation of the inner aspect of the tumor capsule. (D) Follicular carcinoma with vascular invasion with tumor attachment to the endothelium.

nodular hyperplasia, or other lesions. Although two or more adenomas can occur in the same gland, they are nearly always solitary, and a clonal origin has been supported by several studies.^{12,13} Adenomas present as painless lumps, although tracheal compression or pain due to hemorrhage may occur. The tumors are round or oval measuring between 1 and 3 cm and show a homogeneous surface with no internal lobulation. They are typically surrounded by a fibrous capsule of variable thickness, and their color depends on the degree of vascularity, follicular architecture, and amount of colloid. Hemorrhage, fibrosis, calcification, and ossification are less common than in hyperplastic nodules (Fig 2A). Necrosis is rare, but it may be seen as a complication of FNAB, especially in oncocytic lesions. The

tumor cells are monomorphous and polygonal with round to oval normochromatic nuclei.

In the conventional type, several architectural patterns are recognized: (1) In the *trabecular/solid (embryonal)* pattern, the tumors are very cellular with diffuse trabecular or solid architecture and few or no follicles. They resemble the prefollicular stage of thyroid development. (2) In the *microfollicular (fetal)* pattern, the follicles are smaller than in the surrounding gland and contain little colloid. (3) In the *normofollicular (simple)* pattern, the size of the follicles is similar to those of the nonneoplastic gland. (4) In the *macrofollicular (colloid)* pattern, the follicles are larger than the normal gland and contain large amounts of colloid, thus making the distinction

from hyperplastic nodules more difficult.¹⁴ The differential diagnosis includes (1) dominant hyperplastic nodule, (2) minimally invasive follicular carcinoma, and (3) encapsulated follicular variant of PC. The typical uncomplicated adenoma lacks the internal lobulation of nodular hyperplasia. The diagnosis of adenoma should be favored over dominant hyperplastic nodule if the lesion is single, if it is completely encapsulated (Fig 2B), if it compresses the surrounding gland, or if it has a microscopic appearance that differs from the rest of the gland. On the other hand, inflammation, Sanderson's polsters (papillary projections within dilated follicles), and smaller nodules of similar

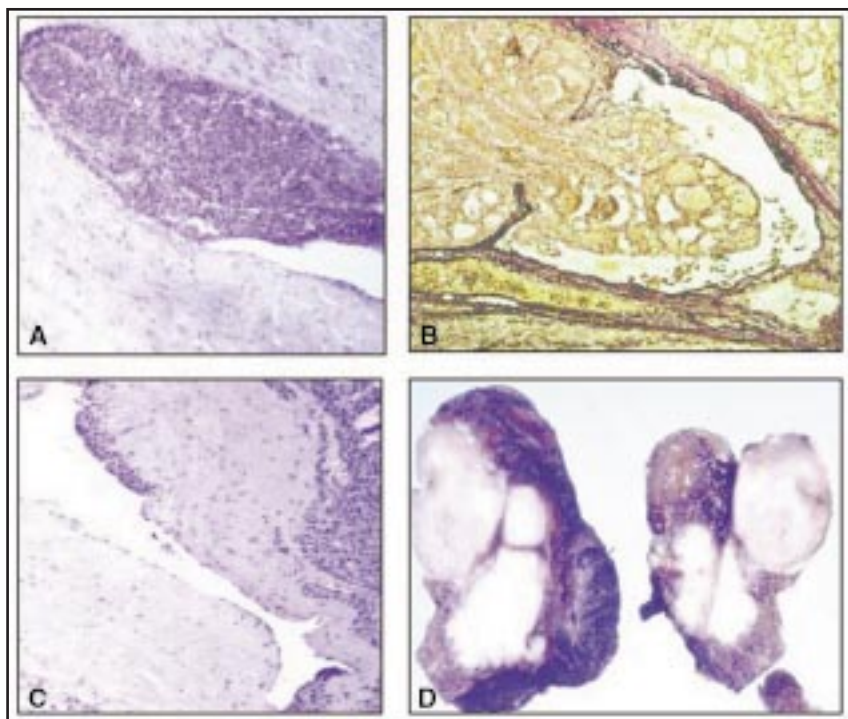
appearance in the rest of the gland suggest the diagnosis of hyperplastic nodule. Some adenomas have special histologic features of no clinical significance: oncocytic or cell adenoma, adenoma with clear cell change, adenoma with bizarre nuclei, hyalinizing trabecular adenoma, adenolipoma, adenochondroma, atypical adenoma, adenoma with papillary hyperplasia, and toxic adenoma.^{2,11}

Follicular Carcinoma

Follicular carcinoma is a malignant epithelial tumor with follicular cell differentiation, but it lacks features typical of other specific

types of thyroid malignancy.² This definition excludes the following entities: follicular variant of PC (PC with predominant or exclusive follicular architecture), follicular oncocytic carcinoma, and poorly differentiated "insular" carcinoma. Follicular carcinoma typically presents as a solitary "cold" nodule without cervical adenopathy or signs of hyperthyroidism. In contrast to PC, it is unusual for follicular carcinoma to be clinically occult, although distant metastases, particularly to the bone, can be the first manifestations of the disease.^{13,15-17} In non-iodine-deficient areas, follicular carcinoma constitutes 5% to 15% of all thyroid malignancies. In iodine-deficient areas, however, the relative incidence reaches 30% to 40% of all thyroid cancers. From morphologic and prognostic standpoints, follicular carcinoma is divided into two major categories on the basis of the degree of invasion: minimally invasive and widely invasive.^{2,11,15}

Minimally Invasive Follicular Carcinoma (MIFC): The gross appearance of MIFC is similar to follicular adenoma, but the peritumoral capsule tends to be thicker and more irregular. MIFC is typically larger than 1 cm and is light tan to brown in color. It has a solid, bulging cut surface, microfollicular architectural growth pattern, and secondary hemorrhagic, cystic or fibrotic changes. The diagnosis of malignancy requires the demonstration of unequivocal capsular and/or vascular invasion. To be considered as unequivocal capsular invasion, the tumor must penetrate the entire thickness of the capsule.



Figs 3A-D. — (A) Follicular carcinoma (high power of Fig 2D). (B) Follicular carcinoma. Elastin stain highlights the disruption of the vessel wall by the intravascular component of the tumor. (C) Follicular carcinoma. Note small intravascular follicular carcinoma attached to the vessel wall. (D) Extensive invasion of surrounding tissue.

Irregularities of contour along the inner border or clusters of follicular cells embedded within the capsule are insufficient (Fig 2C). To qualify as vascular invasion (Figs 2D and 3A-B), the neoplastic cells should project into the lumen of a large caliber vessel, attaching to its wall in a thrombus-like fashion and obliterating the lumen either partially or totally (Fig 3C). The differential diagnosis of MIFC includes follicular adenoma, dominant nodule of nodular hyperplasia, follicular variant of PC, and tubular-follicular variant of medullary carcinoma. The most common metastatic locations are lung and especially bone (femur, pelvis, sternum, and skull). The overall prognosis of MIFC is excellent with a cure rate of over 95%.

Widely Invasive Follicular Carcinoma (WIFC): Gross examination reveals extensive invasion of surrounding tissue and often the lack of a peritumoral capsule (Fig 3D). Microscopically, most tumors exhibit features suggestive of malignancy such as solid areas, trabecular pattern, high mitotic activity, marked nuclear anaplasia, and necrosis. WIFC has an 80% metastatic rate (lung, bone, brain, and liver) and a 20% mortality rate.¹⁸⁻²¹

Cytopathology of Follicular Neoplasms

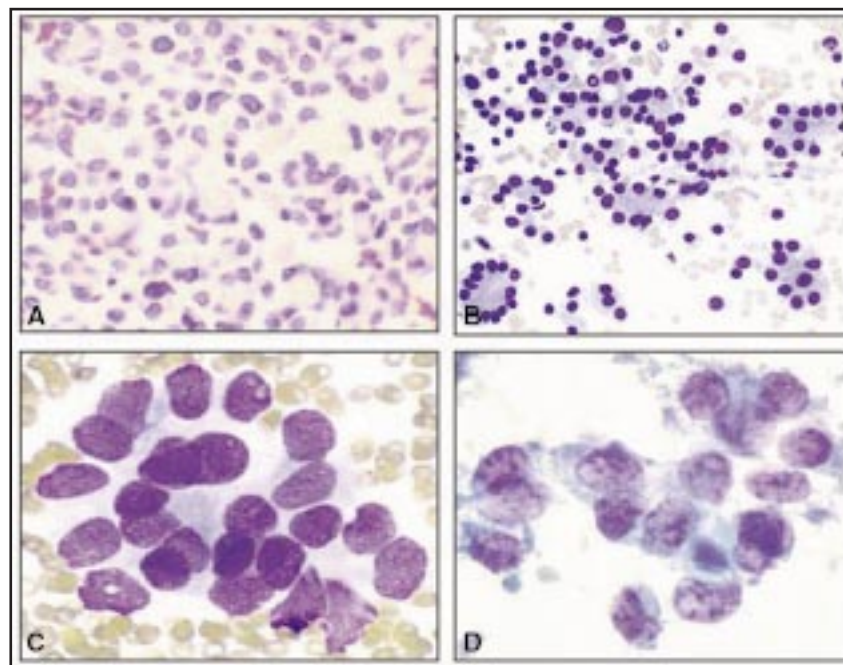
The diagnostic cytologic criteria of follicular adenoma overlap with those of well-differentiated follicular carcinoma. Therefore, the noncommittal terminology of *follicular neoplasm* is commonly used. FNABs of follicular neo-

plasms are typically hypercellular showing little or no colloid (Fig 4A). The cells are found singly or are arranged in microfollicles or syncytial groups with frequent nuclear crowding and overlapping. They have scant cytoplasm, slightly enlarged nuclei, and fine chromatin. Rarely, macrofollicles can also be noted (Fig 4B-C). The main diagnostic pitfalls are hyperplastic adenomatous nodules, follicular neoplasms of Hürthle cell (oncocytic) type, and the follicular variant of PC. Aspirates from poorly differentiated follicular carcinomas are cellular and have similar architectural features to well-differentiated tumors. However, their cells display typical features of

malignancy such as enlarged nuclei, irregular nuclear membrane, nuclear hyperchromasia, and prominent nucleoli (Fig 4D).⁶⁻⁹

Papillary Carcinoma

Papillary carcinoma is a malignant epithelial tumor with follicular cell differentiation characterized by distinctive nuclear features.² PC is the most common type of thyroid cancer, with an incidence rate of 65% to 80% in the United States, and constitutes approximately 90% of thyroid cancers in childhood.^{2,22,23} The ratio of PC in women to men is 2:1 to 3:1 in white populations and 10:1 in Japanese populations. In



Figs 4A-D. — Cytologic patterns of follicular neoplasms of the thyroid by FNAB. (A) Microfollicular adenoma, cell block preparation (hematoxylin-eosin stain). (B) Cellular adenoma with microfollicular pattern and syncytial-type tissue fragments exhibiting uniformly enlarged and crowded nuclei (Diff-Quik stain). (C) Follicular carcinoma with larger and crowded nuclei of variable sizes and shapes in follicular pattern (Diff-Quik stain). (D) Follicular carcinoma with enlarged and hyperchromatic nuclei in syncytial-type tissue fragments (Papanicolaou stain).

about 6% of cases, there is a history of previous irradiation to the neck with an average interval of approximately 20 years. Graves' disease, hyperplastic nodules, adenomas, and Hashimoto's disease are found in glands with PC, but a definitive association has not been established. PC has also been reported in a familial form and in association with a variety of diseases. PC typically presents in the third to fifth decades of life and tends to be multifocal. Extrathyroid extension occurs in only one third of cases, although direct extension into the larynx, trachea, esophagus or skin can rarely be seen. Half of the patients have clinically evident lymphadenopathy at the time of presentation, and nodal metastases tend to adopt a papillary pattern even when not well developed in

the primary tumor. The typical PC is whitish, firm, and granular with ill-defined margins (Fig 5A). The size depends on the particular subtype. Blood-borne metastasis, especially to the lung, also occurs but less commonly than in other thyroid malignancies. Other sites include skeletal system, liver, and the central nervous system.

Conventional Papillary Carcinoma

Conventional PC (Figs 5B-C) has complex papillae with a central fibrovascular stalk of variable thickness interspersed with neoplastic follicles that have similar nuclear features, although in various proportions. A fibrous stroma with broad hyaline bands dividing the tumor into irregular lobules is a common

feature (Fig 5B).^{2,24-26} Psammoma bodies or other calcific concretions may be associated with papillae (Figs 6B and 6E). The diagnosis, however, requires the presence of distinct nuclear features (Figs 5D, 6A, and 6D). Nuclei often overlap and are larger than normal, are round or slightly oval with indentations, folds, pseudoinclusions (Fig 6C), and grooves.¹⁴ Another important feature is the empty appearance of the nucleus known as Orphan Annie Eyes. Mitotic figures are rare. If present in significant numbers, they may indicate poor differentiation and aggressive behavior.

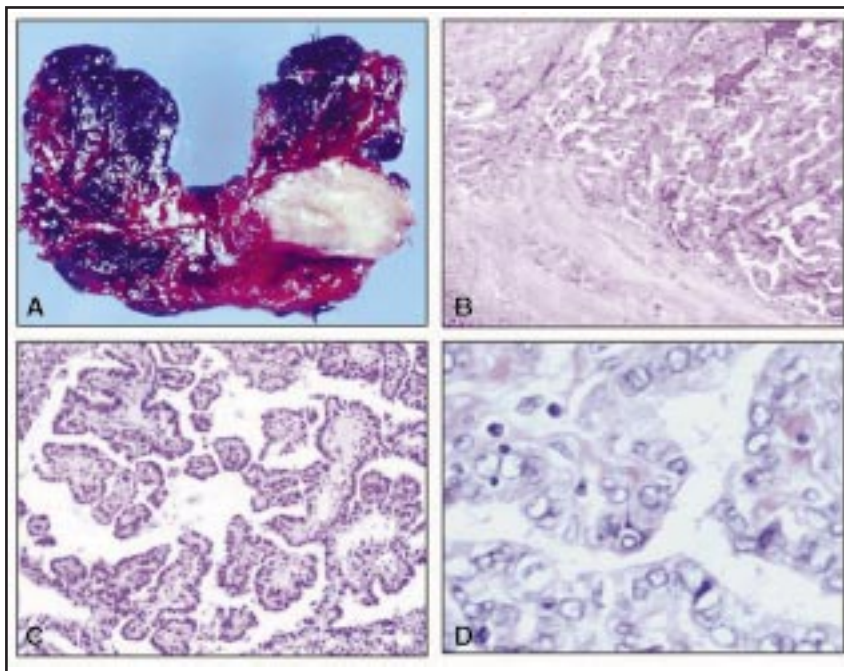
Papillary Carcinoma Variants

Papillary Microcarcinoma:

This tumor, also known as occult sclerosing carcinoma or nonencapsulated sclerosing tumor, usually measures 1.0 cm or less and is found incidentally in approximately 10% of population-based autopsy studies and in 6% in surgical specimens (Fig 7A). It typically has a scar-like configuration with neoplastic cells around the fibrotic area.²⁷

Encapsulated Variant: Approximately 10% of PC is surrounded by a fibrous capsule that may be intact or focally infiltrated by tumor growth. They are associated with nodal metastases in 25% of cases, but blood-borne metastases are rare, and the survival rate is nearly 100%.^{2,11}

Follicular Variant: This tumor has a predominantly or exclusively follicular growth pat-



Figs 5A-D. — Papillary carcinoma. (A) Gross appearance of a single focus invading the thyroid capsule. (B) Fibrotic bands (lower left). (C) Papillae. (D) Nuclear clearing and nuclear grooves.

tern but with cells that have the typical nuclear features of PC (Fig 7B). There is an encapsulated form in which capsular and/or vascular invasion can be seen.

Solid/Trabecular Variant: This is a rare tumor with typical nuclear features of PC but with solid and/or trabecular appearance.

Diffuse Sclerosing Variant: In this tumor, one or both lobes are diffusely replaced by numerous small papillary formations located within intrathyroidal, cleft-like spaces (probably representing lymph vessels), extensive squamous metaplasia, numerous psam-

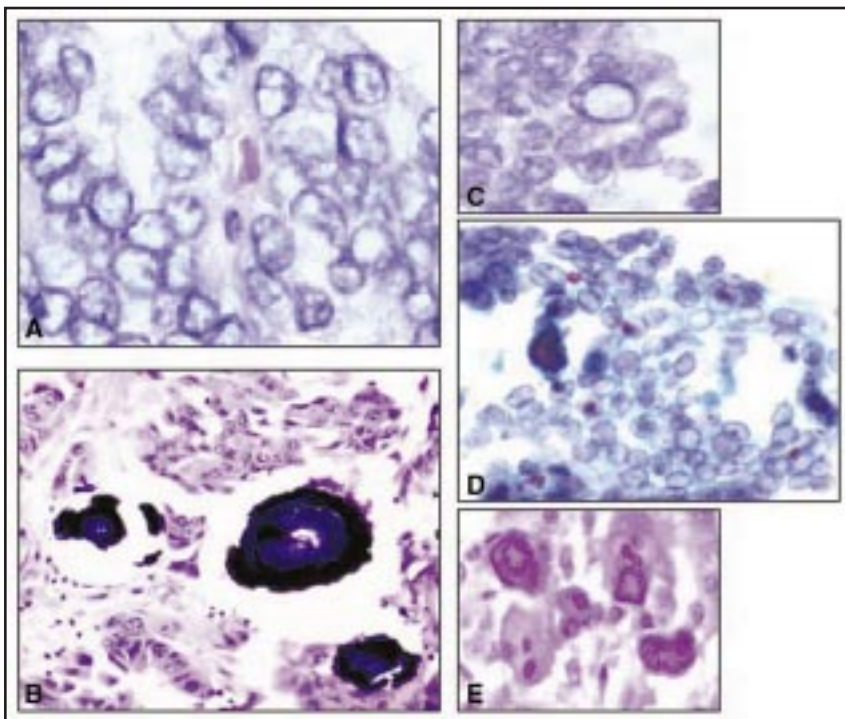
omma bodies, and prominent lymphocytic infiltration and fibrosis.

Tall Cell and Columnar Cell Variants: The incidence of these tumors is approximately 10%, and they tend to occur in older patients. They are usually large (more than 5 cm) and show frequent extrathyroidal extension and vascular invasion. In the tall cell variant (Fig 7C), papillae are well formed and covered by cells twice as tall as they are wide that have abundant acidophilic cytoplasm similar to oncocytes. Mitoses are frequent. In contrast to both the conventional and tall cell forms of PC, columnar cell carcinomas (Fig

7D) have prominent nuclear stratification, and nuclei may lack the typical features of PC. Separation of these two histopathologic entities may be justified on the basis of molecular analyses. Loss of heterozygosity for chromosome 1 (D1S243) and the p53 gene (TP53) have been reported in the tall cell variant but not in the columnar cell variant.²⁸⁻³⁰

Cytopathology of Papillary Carcinoma

Cytologic specimens obtained by FNAB are typically hypercellular with cells organized in monolayered sheets, papillary fragments with branching fronds, and syncytial-type tissue fragments with or without follicles (Figs 8A-C). The amount of colloid is minimal and appears as thick, ropy, or stringy (Fig 8A). The cells are low-columnar or cuboidal showing enlarged, irregular, crowded nuclei with loss of polarity and pale "powdery" or "dusty" chromatin, occasional chromocenters, frequent nuclear grooves and intranuclear pseudo-inclusions (cytoplasmic invaginations).^{6,9} The cytoplasm is variable in size and may appear pale, foamy, vacuolated, dense, or finely granular, mimicking that of Hürthle cells (Fig 8D). Psammoma bodies and multinucleated giant cells may also be identified. A difficult diagnostic problem arises in cystic PC, cystic degeneration, and follicular variant of PC. In cystic PC, numerous lymphocytes, foamy macrophages, and inflammatory debris with insufficient representative cells may lead to a false-negative diagnosis. The follicular vari-



Figs 6A-E. — Papillary carcinoma. (A) Higher magnification of nuclei with clearing of the nuclear chromatin. (B) Psammoma bodies. (C) Intranuclear pseudo-inclusion. (D) Cytology. Note syncytial fragment of papillary carcinoma cells with nuclear clearing or pale chromatin, nuclear grooves, intranuclear pseudo-inclusions in microfollicular pattern (Papanicolaou stain). (E) Early stages of psammoma bodies.

ant of PC with prominent micro-follicles and focal nuclear features typical of conventional PC may be misinterpreted as a follicular neoplasm. Diagnostic pitfalls include nodular hyperplasia, papillary hyperplasia, follicular neoplasms, oncocytic tumors, and medullary carcinoma.

Poorly Differentiated Carcinomas

Some carcinomas that arise from follicular cells are not easily categorized and occupy an intermediate place (both morphologically and behaviorally) between the well-differentiated follicular and PCs and the undifferentiated (anaplastic) carcinomas.³⁰⁻³³

Insular Carcinoma

The incidence of insular carcinoma (IC) varies with geographic location. IC incidence is common in Paraguay but rare in the United States. IC is slightly more common in women, and the mean age at the time of the initial diagnosis is 55 years. The tumor is solid and grayish white, and it often exhibits foci of necrosis. Most tumors measure over 5 cm at the time of diagnosis and may show an invasive type of growth with extrathyroidal extension and blood vessel invasion. The most distinctive histologic feature is the presence of well-defined, round to oval nests (insulae) composed of homogeneous small cells with round nuclei and scant cytoplasm (Figs 9A-B).^{2,11} Mitoses are

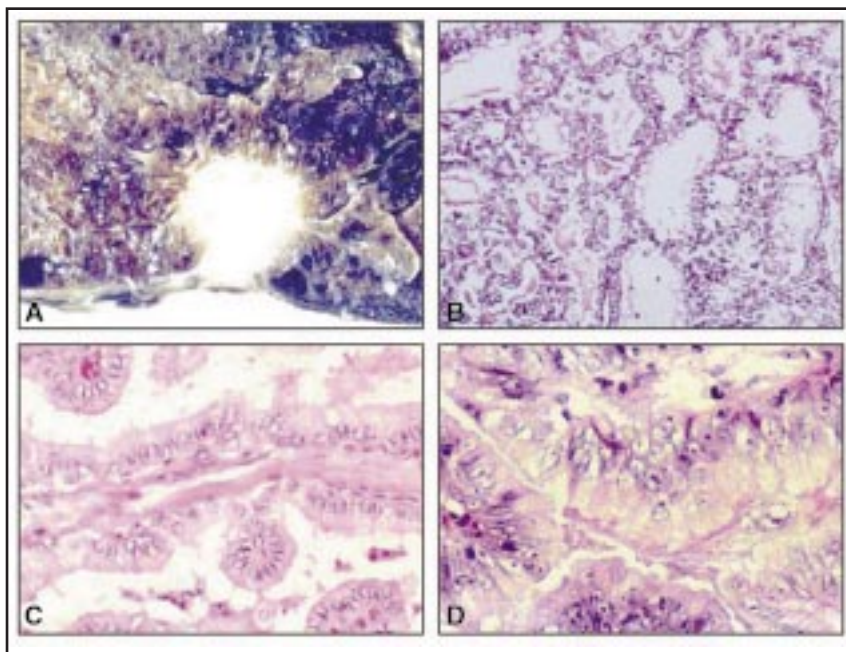
variably present, and foci of necrosis are frequently in the center of the insulae and around blood vessels. This tumor can be confused with medullary carcinoma and other neuroendocrine neoplasms because of its carcinoid-like insular configuration. It may be misdiagnosed as undifferentiated (anaplastic) carcinoma when the predominant pattern of growth is solid, but the tumor cells should be positive for keratin and thyroglobulin and negative for calcitonin. IC is an aggressive and often lethal tumor with common metastases, both to regional lymph nodes and to distant sites (particularly lung and bone). IC is viewed by the World Health Organization Committee as a morphologic variant of follicular carcinoma.

Other Poorly Differentiated Carcinomas

Some thyroid carcinomas share with IC the presence of well-defined nests, predominantly solid pattern, mitotic activity, and necrosis but are composed of larger cells with increased nuclear:cytoplasmic ratio. Some tumors have nuclear features similar to those of PC, and others have the architectural configuration of a follicular carcinoma or the oncocytic features or mixtures of follicular, papillary, oncocytic, and clear cell foci.^{2,11}

Cytopathology of Poorly Differentiated Carcinomas

Cytologic specimens from poorly differentiated carcinomas are highly cellular and often have a necrotic background. Trabeculae



Figs 7A-D. — Papillary carcinoma. (A) Papillary microcarcinoma (occult papillary carcinoma), gross appearance. (B) Follicular variant with typical nuclear features of papillary carcinoma with follicular growth pattern. (C) Tall cell variant with cells as high as they are wide. (D) Columnar variant with pseudostratification and marked atypia of tumor nuclei.

and/or cell clusters are sometimes associated with microfollicles. Cells have poorly defined, occasionally vacuolated cytoplasm and mild to moderate nuclear atypia with occasional intranuclear pseudoinclusions and grooves.⁶⁻⁹

Undifferentiated (Anaplastic) Carcinoma

Anaplastic carcinoma (AC) is a highly malignant tumor that appears partially or totally undifferentiated, although evidence of epithelial differentiation can be found by immunohistochemistry or electron microscopy.^{32,33} AC is also known as pleomorphic carcinoma, sarcoma-

toid carcinoma, metaplastic carcinoma, and carcinosarcoma (Figs 10A-B) and is characteristically a tumor of elderly individuals with a mean age at the time of the initial diagnosis of 60 to 65 years and a ratio of men to women of 1:3 to 1:4. Below 50 years of age, the diagnosis of AC should be made with caution.

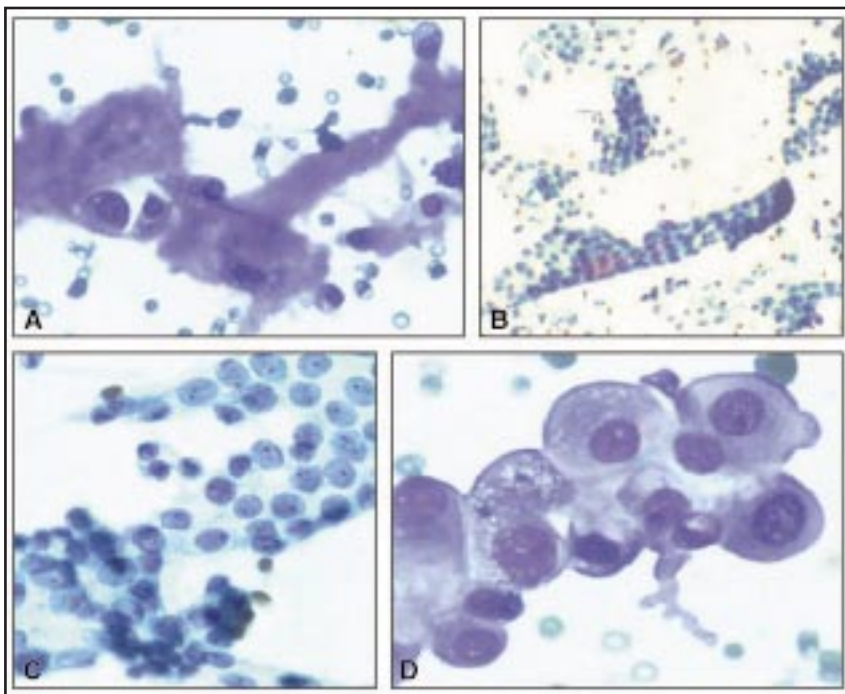
The tumor presents as a rapidly enlarging neck mass (within a few weeks to a few months) that in half of the cases produces compression signs such as dyspnea, dysphagia, and hoarseness. Extrathyroid extension, invasion of major vessels and nerves of the region, and spread into the larynx, trachea, and esophagus are common.

Metastatic nodes are usually embedded in the tumors mass, and blood-borne distant metastases are frequent, especially to the adrenal glands, lung, and digestive tract. AC is fatal in most cases; the longest survival time is 2.5 years.^{34,35}

Necrosis and hemorrhage are frequent, and metaplastic cartilage or bone can be seen. Three distinct histologic patterns are widely recognized (squamoid, spindle cell, and giant cell), and transitions and intermediate forms among them often occur. The spindle cell pattern is indistinguishable from a true sarcoma (fibrosarcoma or a malignant fibrous histiocytoma). The giant cell pattern is characterized by marked pleomorphism and numerous tumor giant cells with bizarre (sometimes multiple) hyperchromatic nuclei. In the squamoid type, there is strong expression of both high- and low-molecular-weight keratins. Spindle and giant cell foci generally lack high-molecular-weight keratins but may show variable reactivity for low-molecular-weight cytokeratin.

Oncocytic (Hürthle Cell) Tumors

Oncocytic tumors are composed exclusively or predominantly (more than 75%) of follicular cells exhibiting oncocytic features (Fig 11A).² The oncocyte has an abundant granular acidophilic cytoplasm containing a large number of mitochondria (Fig 11B). Most authors consider that oncocytic tumors have gross, microscopic, behavioral, cytogenetic, and perhaps etiopathogenetic features that



Figs 8A-D. — Cytologic patterns of papillary carcinoma by FNAB. (A) Thick colloid (Diff-Quik stain). (B) Cellular aspirate with papillary and syncytial type tissue fragments and loose cells (Papanicolaou stain). (C) Syncytial sheet of cells with loss of nuclear polarity, enlarged nuclei, micronucleoli, and nuclear clearing (Papanicolaou stain) (D) Cells of papillary carcinoma with abundant dense and occasionally vacuolated cytoplasm mimicking oncocytic tumors (Papanicolaou stain).

justify their separation from other neoplasms.³⁶

Oncocytic (Hürthle Cell) Adenoma

Oncocytic adenomas are encapsulated, solitary thyroid neoplasms that are round to oval with a homogeneous brown color (due to the cytochrome content of the mitochondria)^{36,37} and frequent calcification, hemorrhage, cystic change, and central scarring. The tumor may undergo a massive infarct-type necrosis, either spontaneously or after FNAB. The pattern

of growth is usually follicular, but it also can be trabecular or solid. Oncocytic cells have vesicular nuclei, and atypia is not uncommon. Ultrastructurally, some mitochondria are markedly abnormal. Immunoreactivity for cytokeratin and thyroglobulin is less intense than in conventional follicular cells.

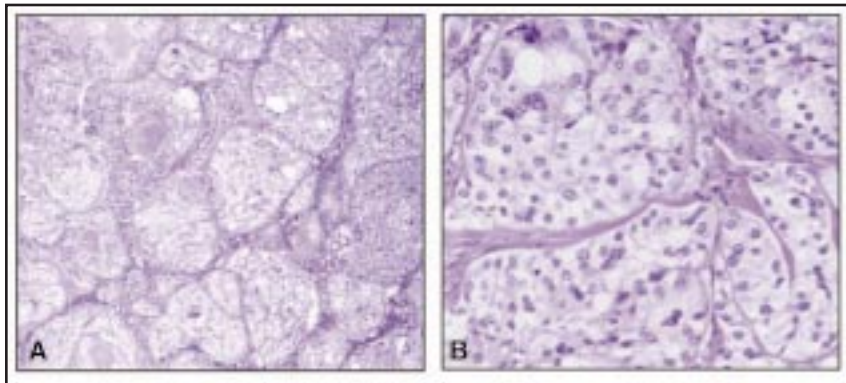
Oncocytic (Hürthle Cell) Carcinoma

Oncocytic carcinoma is a malignant thyroid neoplasm composed exclusively or predominantly (more than 75%) of oncocytes.² It

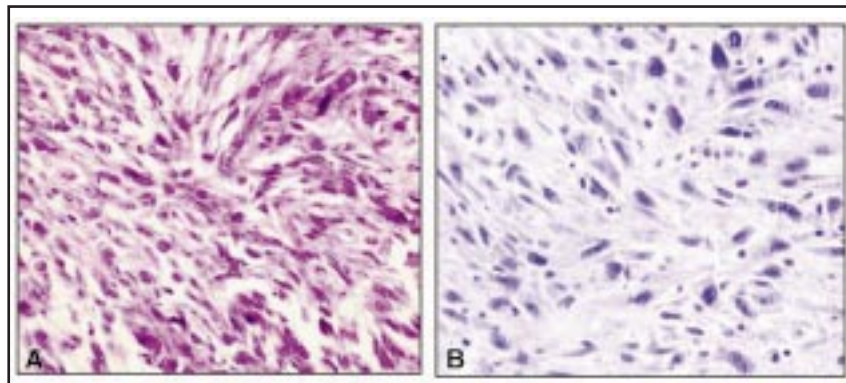
accounts for 2% to 3% of all thyroid carcinomas and 20% of follicular carcinomas. Oncocytic carcinoma is more common in women, and the mean age at the time of initial diagnosis is 55 years (a decade older than in oncocytic adenoma). Degenerative changes are more common than in adenomas. Minimally invasive oncocytic carcinomas possess a complete capsule (encapsulated form). However, widely invasive carcinomas often invade the capsule as sharply outlined nodules that connect with each other and with the main tumor mass, but they may appear as separate tumors. The most common locations for metastases are lung and bone, followed by regional lymph nodes. Some of these metastases occur late in the course of the disease (up to 10 years or more). The overall 5-year survival rate is between 50% and 60%, depending on the degree of invasion. The differential diagnosis includes parathyroid oncocytoma (benign or malignant) and the oncocytic variant of medullary carcinoma.

Cytopathology of Oncocytic Tumors

As in conventional follicular neoplasms, Hürthle cell adenoma and well-differentiated carcinoma cannot be reliably distinguished on cytologic grounds. Generally, Hürthle cells are discohesive, large, and polygonal with granular cytoplasm (Figs 11C-D). The nucleus is large and round to oval with fine chromatin and prominent nucleoli. Binucleation and marked nuclear atypia are common. Aspirates are hypercellular with cells either



Figs 9A-B. — Poorly differentiated carcinoma. (A) Insular carcinoma with islands of tumor cells separated by bands of fibrotic stroma. (B) Insular carcinoma (higher magnification).



Figs 10A-B. — Undifferentiated (anaplastic) carcinoma. (A) Spindle cells in storiform growth pattern. (B) Prominent hyperchromatism and atypia of tumor cells.

singly or in loose aggregates, minimal or no colloid, and no lymphocytes or conventional follicular cells in the background. In Hürthle cell carcinoma, pleomorphism may be prominent. Occasional intranuclear pseudoinclusions and small oncocytic cells with high nucleus:cytoplasm ratio may be seen. The differential diagnosis includes nonneoplastic lesions containing Hürthle cells (eg, nodular hyperplasia with oncocytic metaplasia and chronic lymphocytic Hashimoto's thyroiditis and the oncocytic variant of PC).³⁸

Tumors With Special Features

Clear Cell Features

These are primary thyroid neoplasms in which 75% or more of the tumor cells show marked cytoplasmic clearing due to the presence of cytoplasmic vesicles (dilated mitochondria, endoplasmic reticulum, or Golgi apparatus), glycogen, lipid (lipid-rich adenoma), mucin (signet-ring cell carcinoma), or thyroglobulin.^{2,11}

Mucinous Features

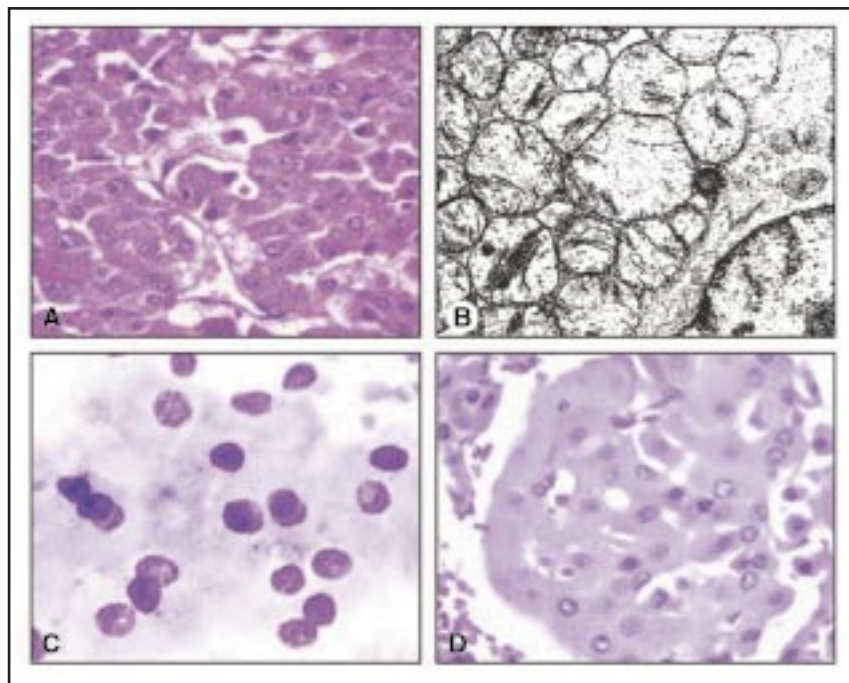
Extracellular hyaluronic acid and intracytoplasmic acid glycoproteins can be detected in signet-ring follicular adenoma, follicular carcinoma with signet-ring features, mucoepidermoid carcinoma, sclerosing mucoepidermoid carcinoma with eosinophilia, PC, medullary carcinoma, and undifferentiated carcinoma. Rare mucinous carcinomas show a glandular archi-

tecture similar to pulmonary or gastrointestinal malignancies, and transitions to areas with follicular differentiation can be seen. Thyroglobulin expression may be negative in the mucinous areas.

Squamous Features

Squamous metaplasia is rare in follicular and medullary carcinomas but is found in approximately 30% of PCs. The term *squamous cell carcinoma* is reserved for those tumors with obvious malignant squamous differentiation that is sometimes mixed with undifferentiated areas or mucin production (adenosquamous carcinoma). Secondary involvement by a nonthyroidal squamous cell carcinoma

should be ruled out. Primary *mucoepidermoid carcinomas* seem to be related to PC. The so-called *sclerosing mucoepidermoid carcinoma with eosinophilia* is a low-grade malignant neoplasm of unclear origin that arises in a setting of Hashimoto's thyroiditis and is composed of nests of pleomorphic squamoid cells embedded in a dense fibrohyaline stroma infiltrated by eosinophils and often containing mucin. A rare intrathyroidal or perithyroidal carcinoma thought to arise from thymic or branchial pouch derivatives is known as *carcinoma showing thymus-like element (CASTLE)*. This tumor has a lobular growth pattern, lymphocytic infiltration, and occasional perivascular spaces.



Figs 11A-D. — Oncocytic tumor. (A) Oncocytic cells with eosinophilic cytoplasm. (B) Abnormal mitochondria within oncocytic cells (electron micrography). (C) Cytologic features of oncocytic cells. Note oncocytic cells in large polygonal cellular clusters, abundant granular cytoplasm, and uniform nuclei with macronucleoli (Diff-Quik stain). (D) Clusters of oncocytic cells (cell block).

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