

Proliferative Lesions of the Thyroid and Parathyroid Glands

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THYROID GLAND

INTRODUCTION

Neoplasms can potentially arise within the thyroid gland from any of several cell types including the two glandular parenchymal cells, parafollicular (C-cells) and follicular cells, as well as those associated with lymphatic or blood vessels, nerves, and the stromal fibrous connective tissue. Spontaneous and induced proliferative lesions of the thyroid gland are more common in rats than mice (1, 12, 13, 20, 28, 35).

Hyperplastic or neoplastic changes may involve the thyroid unilaterally or bilaterally. Most focal hyperplastic lesions and small adenomas of follicular or C-cell origin are not grossly visible. Diffuse hyperplasia may be seen as bilateral enlargement accompanied by darker red coloration. Large follicular adenomas are reddish to yellow-grey nodules and may be multiple. Visible C-cell adenomas are white and also may be multiple. Fluid-filled cysts large enough to be seen grossly may occur in follicular adenomas or carcinomas of the macrofollicular pattern. Usually other types of cystic lesions are microscopic. Generally, thyroid follicular carcinomas are very vascular, soft, and resemble the normal red-brown coloration of the thyroid gland while C-cell carcinomas are pale tan to yellow, firm and less vascularized. Both may efface the gland and/or invade the thyroid capsule.

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MORPHOLOGY

FOLLICULAR CELL HYPERTROPHY (Figure 1)

Activity of the thyroid gland varies between individuals of the same sex, age, and strain; males and females; and animals of different ages (12, 13, 21, 26). This variation reflects complex multifactorial interactions which increase or decrease with changes in thyroid stimulating hormone (TSH) production by the pituitary gland. Increases in this hormone result in diffuse physiologic changes seen morphologically as increased vascularity, which is the first change observed, and increased height of the follicular epithelium from cuboidal to tall columnar. Both of these changes are the most consistent histological indicators of thyroid follicular epithelial activity. Decreased staining intensity of colloid, in which it appears pale or slightly basophilic as compared to the usual brightly eosinophilic appearance, is associated with utilization of thyroglobulin in thyroid hyperactivity.

FOLLICULAR CELL HYPERPLASIA (Figures 2, 3, 4)

Follicular cell hyperplasia occurs as a diffuse or focal change, often involving multiple sites in one or both lobes of the thyroid gland. Diffuse hyperplasia frequently is microfollicular in appearance, and the lobes are grossly enlarged and assume a more lobulated shape rather than being smoothly ovoid. Follicular epithelium is hyperchromatic, cuboidal to flattened cuboidal, or may appear more active with tall columnar epithelium having large basophilic ovoid nuclei. There is no cellular atypia or invasion. Follicular cell number per unit area may be increased either by papillary infoldings of epithelium or stratification of follicular lining cells. Follicular lumens in focal hyperplastic lesions may contain an increased

amount of colloid which can cause compression of adjacent parenchyma, but there is minimal architectural distinction from adjacent thyroid parenchyma and no encapsulation. Hyperplastic foci blend with the adjacent gland and are poorly demarcated. Follicular cysts, in contrast to focal hyperplasia, are sharply demarcated and may be distended with colloid, but are lined by a single layer of flattened epithelium. The thyroid capsular connective tissue may increase in thickness in rats with hyperplastic lesions (34). The lesions are considered to be incapable of autonomous growth and may retain the potential for regression following the withdrawal of the inciting stimulus (4, 12, 13, 21, 26, 30, 31, 35).

FOLLICULAR CELL ADENOMA (Figures 5, 6)

Adenomas are well delineated, minimally to nonencapsulated, expansile and compressive masses (5, 20, 21, 26, 30, 31, 35). There may be homogeneous cellular morphology and architecture within an adenoma, but both differ from the adjacent thyroid gland parenchyma. Adenomas exhibit three patterns or combination of patterns: cystic, papillary, or solid. Solid patterns include macro- or microfollicular types. Colloid is often prominent in the macrofollicular type. Follicular size is variable. The epithelial lining may be single or multiple layers of cuboidal to columnar cells, with an increased nuclear to cytoplasmic ratio. Nuclear hyperchromasia, cytoplasmic basophilia, and nuclear crowding are variably present. Mitotic figures are generally not present.

FOLLICULAR CELL CARCINOMA (Figures 7, 8)

Patterns of cellular arrangement within follicular cell carcinomas include papillary, cystic, macrofollicular, solid (microfollicular), scirrhous or a mixture of patterns within a single mass (6, 20, 26, 30, 31, 35). Solid and follicular areas may appear in the same tumor. Neoplastic follicular cells have large nuclei with prominent nucleoli and usually appear well differentiated. Small solid nests and/or sheets of follicular cells may be intermingled with areas of fibrosis or, occasionally, the follicular cells may be highly pleomorphic and occur in small nests of individualized cells which incite a marked scirrhous reaction. Vascularity within the neoplasm often is a prominent feature although not diagnostic for carcinomas. Necrosis is common. The mitotic index is variable but may be quite high. Variable features include focal mineralization, brown (iron and PAS positive) pigment (32), and cholesterol cleft formation. Encapsulation is variable and the tumor may have a scirrhous capsule with tumor cells penetrating through the capsule. Invasion of the capsule, adjacent tissues, lymphatic and/or blood

vessels, necrosis, and distant metastases may be seen.

C-CELL HYPERPLASIA (Figures 9, 10)

Proliferation of C-cells is common in the rat but quite rare in the mouse (7). Diffuse lesions are common in aging rats and are composed of normal appearing C-cells surrounding follicles, giving the impression of increased interfollicular tissue. Rarely do C-cells accumulate more than two cells deep in diffuse hyperplasia. Transverse sectioning of the thyroid gland results in fewer sections containing proliferative C-cells than longitudinal sectioning when embedded flat. Consistent sampling is imperative to accurately evaluate incidences of C-cell lesions (16).

Small focal hyperplastic lesions occur in the parafollicular area with little compression or distortion of the adjacent follicles. In larger lesions there may be compression of follicles with follicular atrophy and filling of follicles with C-cells. There is no invasion or encapsulation. Normal C-cells are polyhedral to spherical with pale eosinophilic cytoplasm and a centrally located nucleus. C-cells forming hyperplastic foci are morphologically indistinguishable from normal C-cells and these foci of hyperplasia do not exceed five average follicular diameters (13, 16, 17).

C-CELL ADENOMA (Figures 11,12)

C-cell masses greater than five average follicular diameters have been designated adenomas (12, 14, 16, 17, 20). These neoplasms are frequently compressive but do not invade. They are rarely encapsulated, have scant stroma, and are usually discrete, well-circumscribed masses. Neoplastic C-cells are usually indistinguishable from normal C-cells having uniform pale, slightly eosinophilic cytoplasm and spherical centrally located nuclei. Less frequently, the cytoplasm may be more basophilic. Tumor cells are round to oval but may be fusiform in an expanding mass if they are compressed by surrounding cells. Cells may spill over into contiguous follicles or expand a single follicle. The presence of amyloid within the neoplasm is infrequent.

C-CELL CARCINOMA (Figures 13, 14)

Cells in C-cell carcinomas (9, 12, 13, 20) are variably arranged in solid sheets to irregular groups separated by fibrovascular stroma which may have amyloid present. Cellular morphology of the neoplastic cells depends on the degree of differentiation. They may be well differentiated with round to polygonal cells having abundant lightly eosinophilic cytoplasm and round to oval nuclei containing finely stippled chromatin. Alternatively, less differentiated cells

exhibiting more nuclear pleomorphism may be the predominant cell type. Many C-cell carcinomas have markedly pleomorphic cells with increased cytoplasmic basophilia, fusiform shape and many mitotic figures. Hemorrhage in solid tumors is sometimes present. Criteria for malignancy may include invasion of the capsule, adjacent tissue, lymphatic and/or blood vessels, necrosis and distant metastases. These features are critical to assess malignancy in well-differentiated C-cell carcinomas.

DISCUSSION

Borderline proliferative lesions present the most difficulty in the thyroid gland, particularly, when distinguishing between C-cell hyperplasia and adenoma. It is necessary to establish arbitrarily a size criteria to maintain consistency in diagnosis of these two lesions. Compression is not a reliable characteristic to distinguish C-cell adenomas, however, it is the key feature to categorize follicular cell hyperplasia and adenoma with the caveat that colloid-filled follicular cysts may be compressive. For very anaplastic neoplasms, immunohistochemistry and electron microscopy may be necessary to determine the cell of origin.

Goitrogenic compounds, such as ethylthiourea or amitrone, administered to rats have been shown to induce follicular cell hyperplasia which may progress to follicular cell adenomas and carcinomas (21, 29, 30, 31, 35). Amitrone, for example, inhibits peroxidase activity as do many goitrogenic compounds. This inhibition prevents one step in the synthesis of T₃ and T₄ causing release of excessive thyroid stimulating hormone by the pituitary via a negative feedback loop (12, 13, 21, 29). Compounds such as phenobarbital which induce hepatic microsomal enzymes may increase the number of induced thyroid neoplasms by indirectly increasing release of TSH in response to more rapid removal of thyroid hormones from the plasma by enhanced catabolism and excretion (18, 19, 21). Similarly, a leukotriene antagonist (L-649,923) has been reported to cause increased metabolism of plasma thyroxine resulting in stimulation of TSH and thyroid hyperplasia in Sprague-Dawley rats experimentally (27). These and other various manipulations of experimental design to delineate the interactions of goitrogens, thyroid hormone supplementation, thyroid carcinogens, and microsomal enzyme inducers provide evidence that prolonged follicular hypertrophy and TSH stimulation of the thyroid may progress to follicular hyperplasia and neoplasia.

PARATHYROID GLAND

INTRODUCTION

The only parenchymal cell in the rat parathyroid is the chief cell (1, 10, 14, 23). The gland is surrounded by a delicate fibrous capsule and is composed of tightly packed nests of chief cells separated by fine fibrovascular connective tissue septae. No oxyphilic cells are present as in other species (10). Mitotic activity is present in normal parathyroid glandular epithelium. Multinucleate, syncytial chief cells have been reported as a normal finding in untreated rats (10). Syncytial cells are present in variable numbers in different areas of the gland but are most numerous near the periphery. Parathyroid neoplasms are rare in rats (10, 11, 14, 22, 24, 33).

Hyperplastic lesions and adenomas are similar in color grossly and are white to light grey. In diffuse hyperplasia, the parathyroid glands may be bilaterally enlarged and elevated above the surface of the thyroid. Only in focal hyperplasia may the lesion be unilateral. Adenomas are usually small, nodular, solitary masses originating in normal or hyperplastic parathyroid glands. The contralateral gland may be hyperplastic, normal or atrophic. Carcinomas of the parathyroid are extremely rare in rats (10, 22, 33). They may efface the entire parathyroid and/or thyroid gland. They are pale grey-white and may have central necrosis.

MORPHOLOGY

HYPERPLASIA (Figures 15, 16, 17)

Cells within the parathyroid gland may increase in number and become quite large in conditions in which calcium homeostasis is disrupted (23, 24). Chief cells are polygonal and have pale eosinophilic cytoplasm. The nuclei range from round to fusiform and have finely stippled chromatin. The cellular population is generally homogeneous and the glands are bilaterally enlarged in diffuse hyperplasia which may result in compression of adjacent thyroid parenchyma or protrusion above the capsular surface. Occasionally, the fibrous capsule may be thickened. Cells may appear dark or clear depending on the functional state, however, these differences in tinctorial staining quality do not represent two distinct cell types. Focal hyperplasia exhibits similar cellular features with no compression of adjacent parenchyma. There are no distinguishable boundaries and the lesion is unencapsulated.

ADENOMA (Figure 18)

Adenomas may appear similar to focal hyperplasia but are well demarcated from the bordering tissue and are compressive (22). The cellular morphology and/or pattern within the neoplasm is distinct from that of surrounding parathyroid gland. Patterns are varied with solid tumors being most common. Other patterns are papillary or acinar arrangement of cells. Encapsulation may be present. Cytologic features include clear or vacuolated cytoplasm with distinct cellular borders, pleomorphic nuclei and variable number of mitotic figures. A rim of normal or atrophic parathyroid tissue may be present.

CARCINOMA

Parathyroid carcinomas occur so rarely (3,22,33) that none have been reported and confirmed by immunohistochemistry in the National Toxicology Program Data Base. Presumably characteristics of malignancy including anaplasia, necrosis, capsular penetration or distant metastasis as seen with other neoplasms would be applicable to the parathyroid gland carcinomas. One parathyroid carcinoma was reported and described in an OFA rat by Pour et al., 1983 (22). The neoplastic cells in this carcinoma were anaplastic and oval to fusiform in shape. These cells occurred in sheets or nodules within a variable amount of fibrous connective tissue. Criteria for carcinomas of parathyroid were developed from that single description.

DISCUSSION

Two neoplasms diagnosed as parathyroid carcinomas in NTP studies have been shown by immunohistochemistry to be thyroid follicular cell carcinomas. Additional sections of one of these tumors exhibited follicular formation which was not present in the original section thereby strongly suggesting thyroid rather than parathyroid gland origin.

Aged rats with chronic nephropathy frequently may have diffuse bilateral parathyroid hyperplasia. Unilateral and/or focal hyperplasia of the parathyroid does occur but must be diagnosed only after examination of both parathyroids since often only one gland or only a small area of the contralateral gland may be present in a routine transverse section. Adenomas may be functionally active causing the adjacent or opposite gland to sometimes become atrophic. Discrimination between focal hyperplasia and adenoma is difficult and often the key feature separating the two entities is compression which is exhibited by adenomas.

NOMENCLATURE AND DIAGNOSTIC CRITERIA**THYROID GLAND****FOLLICULAR CELL HYPERTROPHY**

1. Diffuse, bilateral
2. Decreased diameter of follicular lumens
3. Large cuboidal to tall columnar epithelial cells
4. Decreased eosinophilia of colloid
5. Increased vascularity
6. Increased number of follicles
7. Physiologic response to Thyroid Stimulating Hormone

FOLLICULAR CELL HYPERPLASIA

1. Focal or diffuse, unilateral or bilateral
2. Noninvasive, nonencapsulated, noncompressive and poorly demarcated
3. Follicle size variable, enlarged follicles may cause compression
4. Increased numbers of cuboidal to columnar, hyperchromatic to vacuolated epithelial cells, sometimes with papillary infolding or slight stratification
5. Increased vascularity

FOLLICULAR CELL ADENOMA

1. Single or multiple, unilateral or bilateral
2. Well-demarcated, non- or minimally encapsulated, compression of adjacent follicles
3. Papillary, follicular, cystic, or solid (microfollicular) patterns often with mixture of two or more patterns
4. Cells usually in a single layer, sometimes in multiple layers
5. Cells cuboidal to columnar with eosinophilic to basophilic cytoplasm, low mitotic index, increased nuclear to cytoplasmic ratio, nuclear hyperchromasia and/or crowding sometimes present

FOLLICULAR CELL CARCINOMA

1. Unilateral or bilateral
2. Papillary, follicular, solid (microfollicular) and cystic patterns often with mixture of two or more patterns

3. Cells may form multiple layers, solid nests and/or sheets
4. Minimal to marked cellular pleomorphism, usually a high mitotic index, prominent vascularity, necrosis and mineralization may be present
5. Fibroplasia, penetration of thyroid gland capsule, local invasion of adjacent tissues and/or vessels, and metastasis indicate malignancy

C-CELL HYPERPLASIA

1. Focal or diffuse, unilateral or bilateral
2. Increased numbers of C-cells present in clusters less than five average follicular diameters or scattered in interfollicular space
3. Minimal compression or distortion of thyroid follicles
4. C-cells large and round to polyhedral with abundant pale eosinophilic cytoplasm and centrally located round nuclei
5. Diffuse lesions surround follicles resembling increased interfollicular tissue

C-CELL ADENOMA

1. Single or multiple, unilateral or bilateral
2. Discrete mass greater than five average follicular diameters
3. Noninvasive, rarely encapsulated, scant stroma, may contain scattered follicles, amyloid present rarely
4. Solid sheets of round to oval to fusiform cells with pale eosinophilic cytoplasm or, infrequently, basophilic cytoplasm, and round to oval centrally located nuclei

C-CELL CARCINOMA

1. Unilateral or bilateral
2. Solid sheets or irregular nests of cells separated by fibrovascular stroma, necrosis may be present, amyloid present rarely
3. Cells vary from round to polygonal with abundant pale eosinophilic cytoplasm and round to oval nuclei to markedly pleomorphic highly fusiform basophilic cells with high mitotic index
4. Penetration of thyroid gland capsule, local invasion of adjacent tissues and/or vessels, and metastasis indicate malignancy

PARATHYROID GLAND

HYPERPLASIA

1. Focal or diffuse, unilateral or bilateral
2. In diffuse lesions, bilateral glandular enlargement is present, compression is sporadic, and encapsulation occurs occasionally
3. Increase in cell number, cellular size may be variable, cytoplasm may be clear or eosinophilic
4. Focal lesions blend with adjacent gland, are unencapsulated and noncompressive

ADENOMA

1. Solitary, well-delineated, compress adjacent tissue, may be encapsulated
2. Solid, papillary, or acinar patterns
3. Cells may have clear to vacuolated cytoplasm and pleomorphic nuclei, variable mitotic index

CARCINOMA

1. Solitary masses of oval to fusiform cells arranged in sheets or nodules separated by fibrous tissue, variable mitotic index, necrosis may be present
2. Penetration of capsule, local invasion of adjacent tissues and/or vessels, and metastasis may occur

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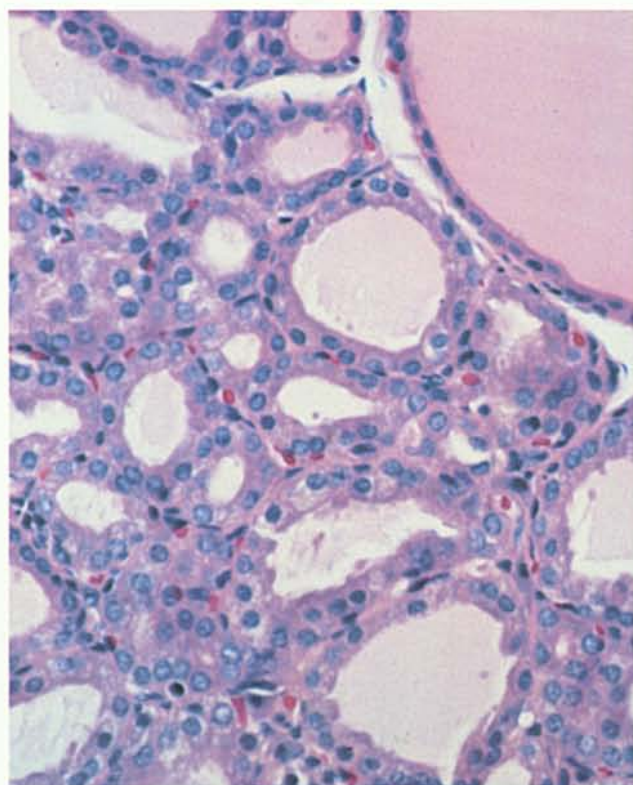


Fig. 1 Follicular Cell Hypertrophy - Diffuse hypertrophy of follicular cells with decreased lumen diameters. (H&E, 205x)

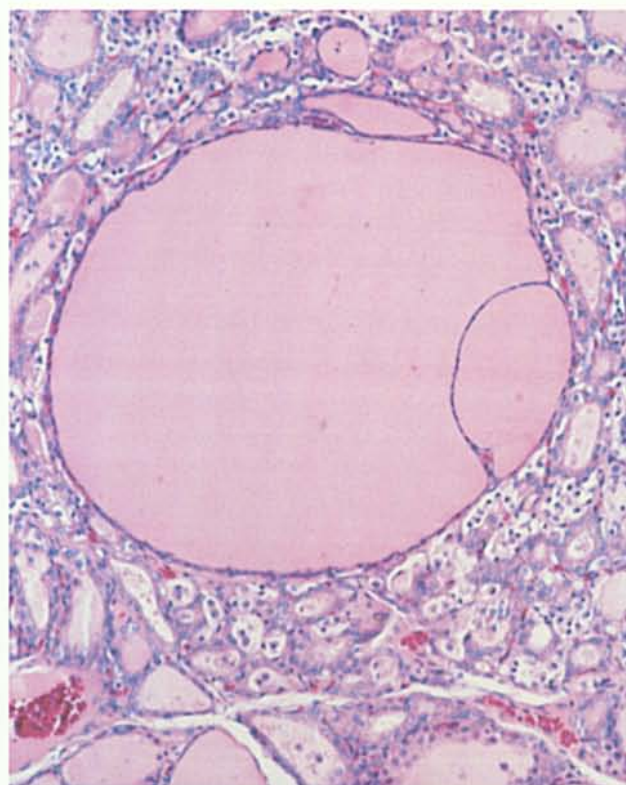


Fig. 2 Follicular Cyst - Cyst distended with colloid and lined by flattened epithelium. (H&E, 82x)

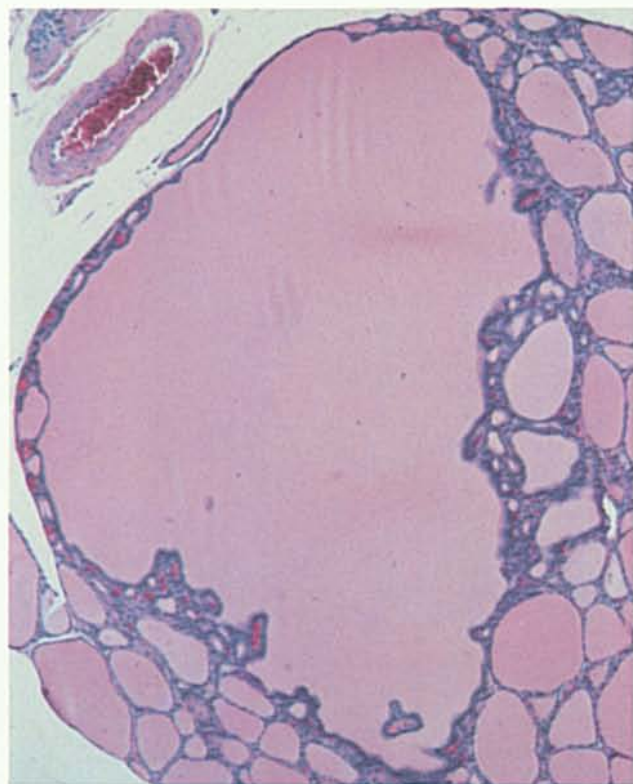


Fig. 3 Follicular Cell Hyperplasia - Focal hyperplasia with increased colloid and papillary infoldings of lining epithelium. (H&E, 41x)

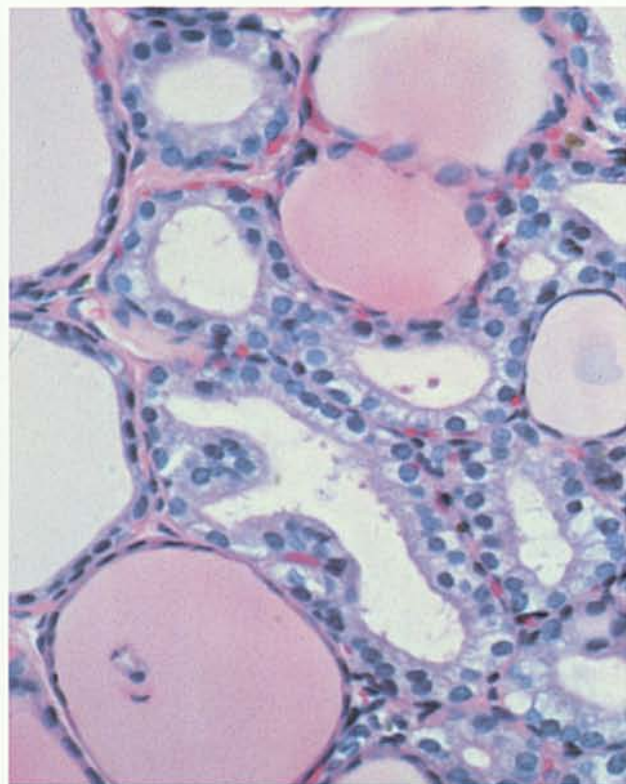


Fig. 4 Follicular Cell Hyperplasia - Diffuse hyperplasia with increased numbers and papillary infolding of lining epithelium. (H&E, 205x)

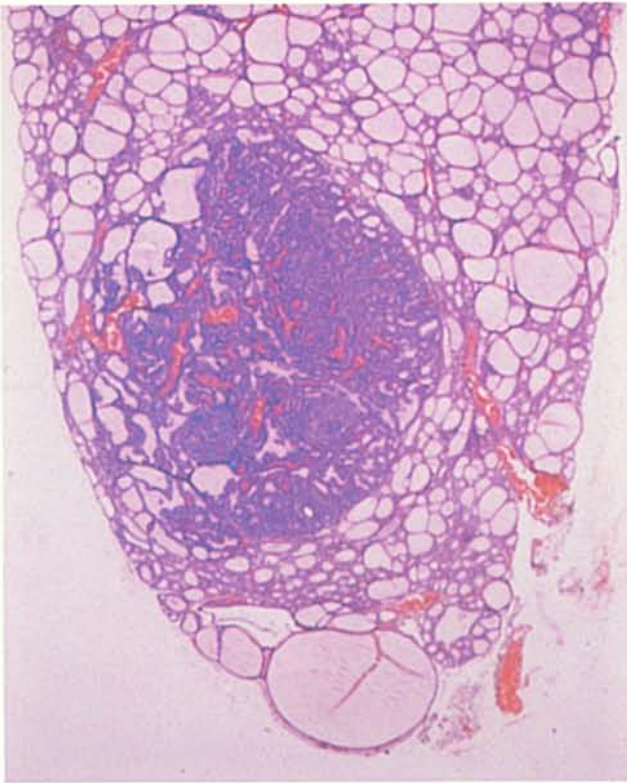


Fig. 5. Follicular Cell Adenoma - Nonencapsulated well-demarcated proliferation of follicular epithelium with compression of adjacent follicles. (H&E, 13.5x)

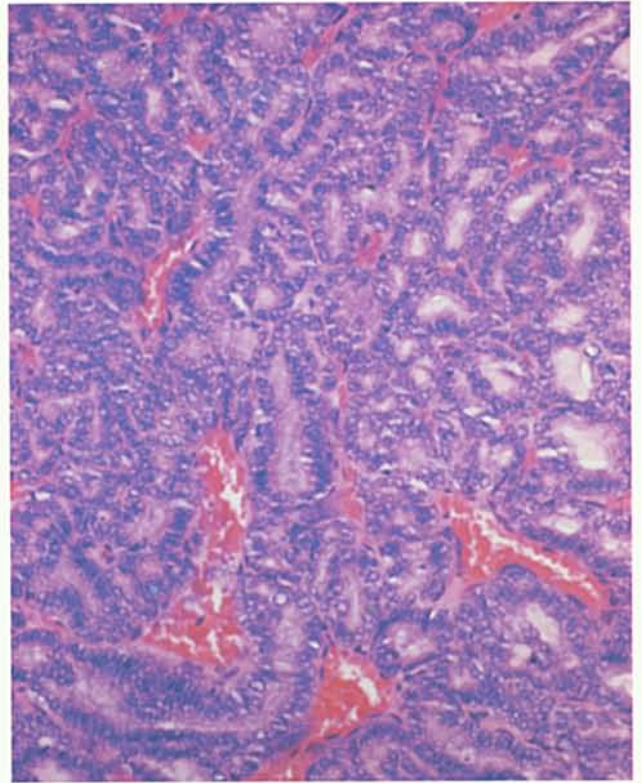


Fig. 6. Follicular Cell Adenoma - Higher magnification of Figure 5 (H&E, 205x)

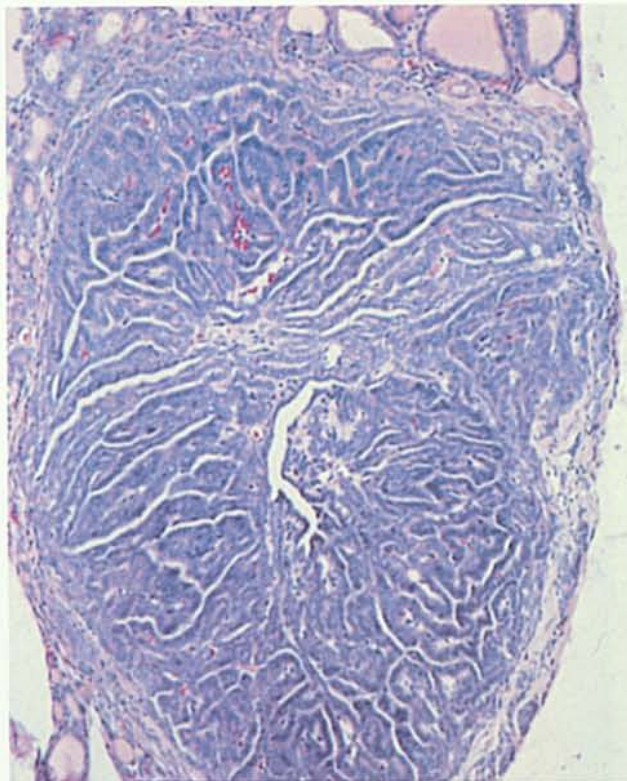


Fig. 7. Follicular Cell Carcinoma - Papillary pattern with cellular pleomorphism and fibroplasia. (H&E, 67.65x)

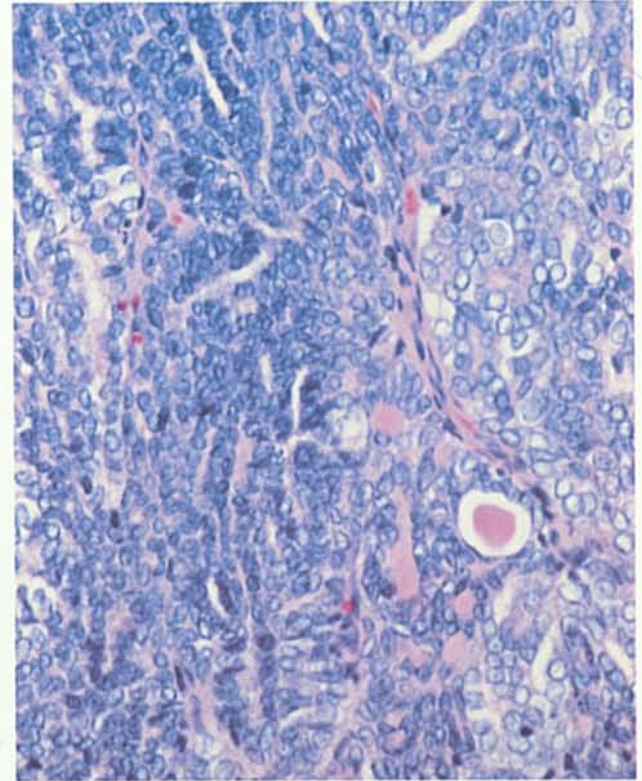


Fig. 8. Follicular Cell Carcinoma - Higher magnification of Figure 7 (H&E, 205x)

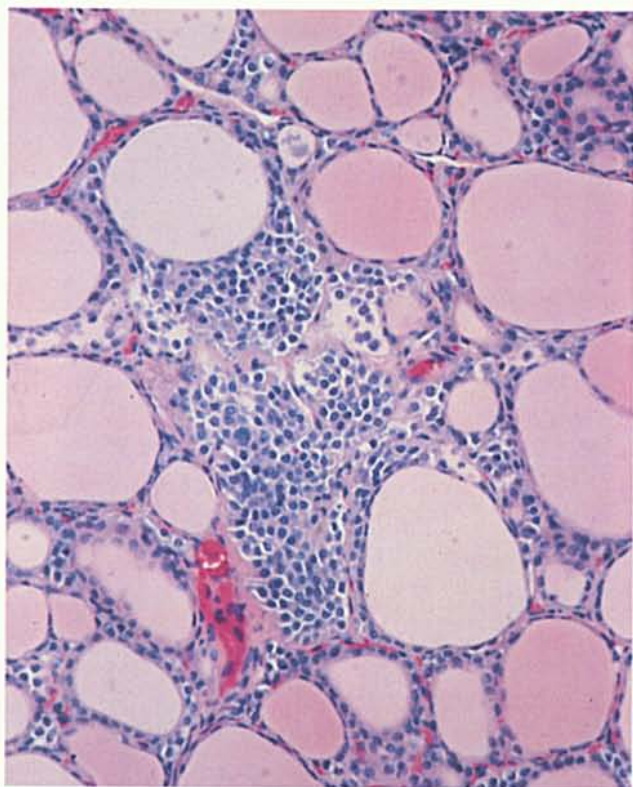


Fig. 9. C-Cell Hyperplasia - Focal hyperplasia of C-cells with minimal compression of thyroid follicles. (H&E, 102.5x)

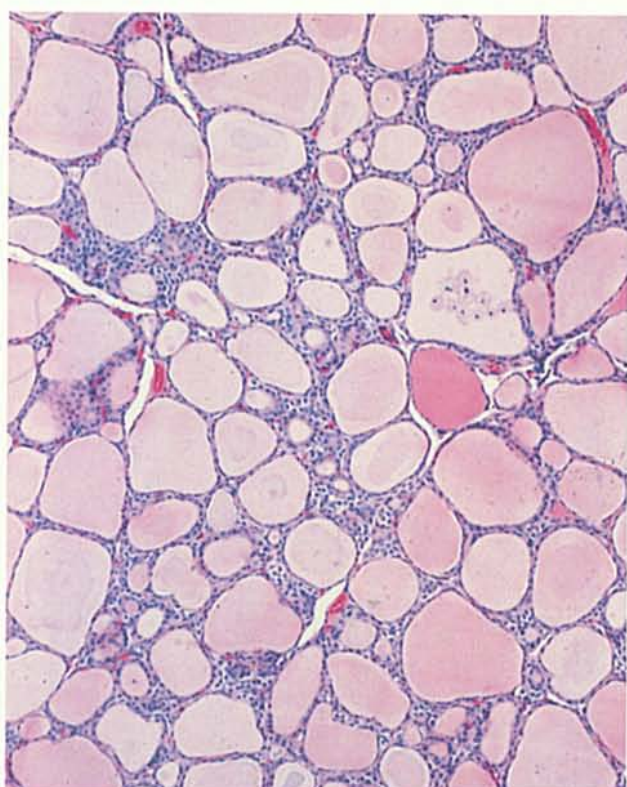


Fig. 10. C-Cell Hyperplasia - Diffuse hyperplasia of C-cells surrounding follicles resembling increased interfollicular tissue. (H&E, 51.25x)



Fig. 11. C-Cell Adenoma - Discrete, nonencapsulated, noninvasive proliferation of C-cells with residual follicles. (H&E, 16.4x)

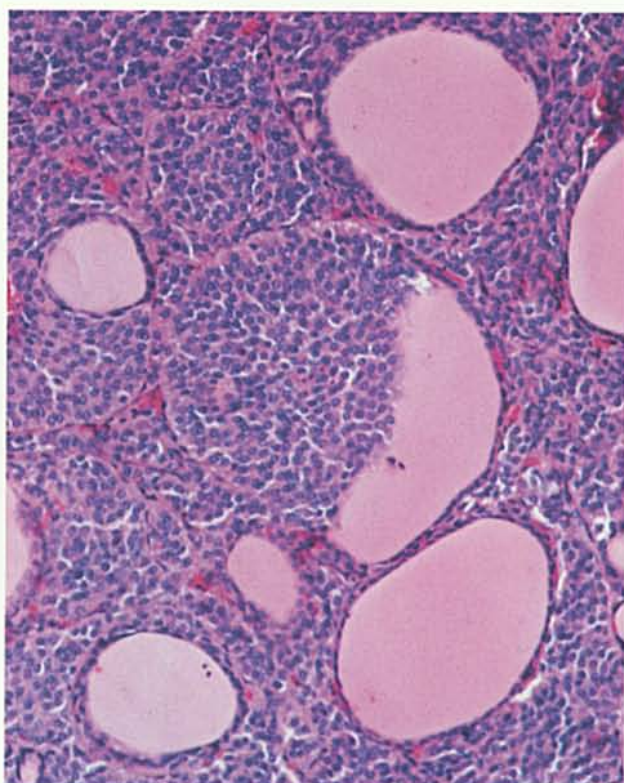


Fig. 12. C-Cell Adenoma - Higher magnification of Figure 11 (H&E, 102.5x)

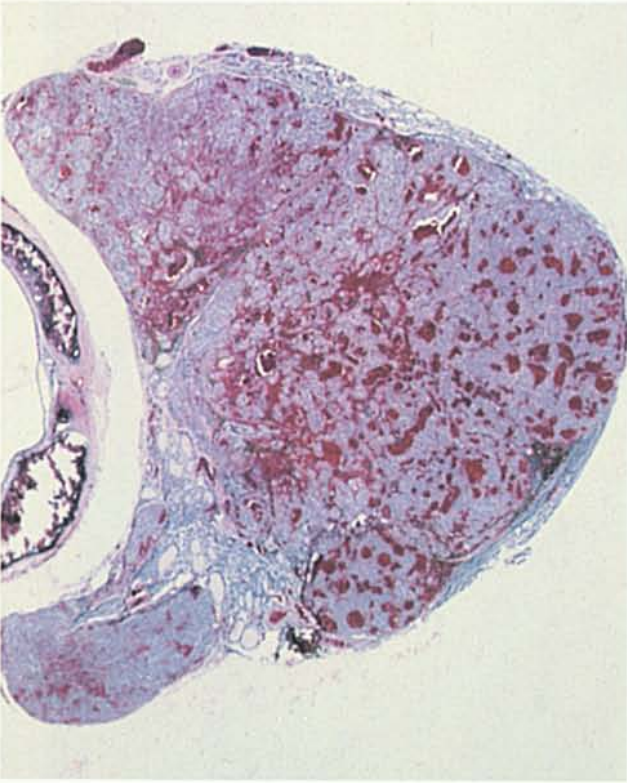


Fig. 13. C-Cell Carcinoma - Solid sheets of proliferating C-cells with invasion into the capsule of the thyroid gland. (H&E, 10.25x)

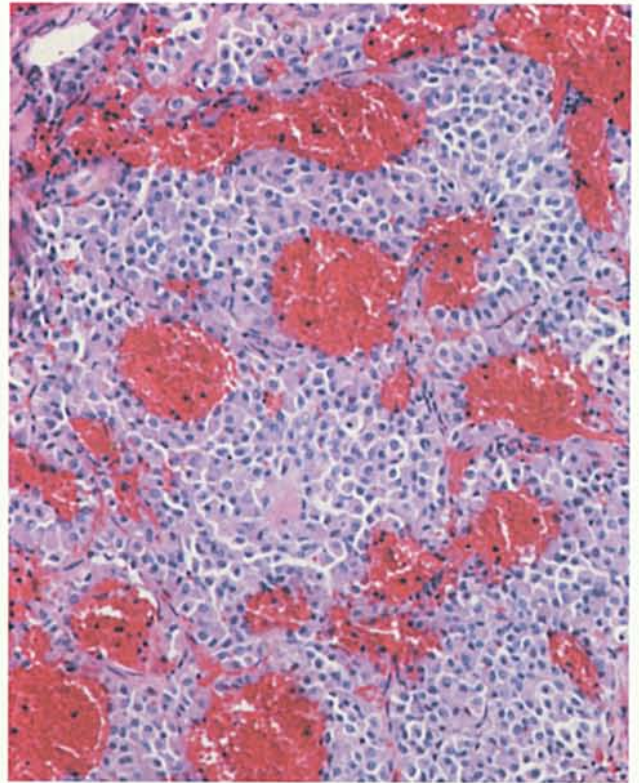


Fig. 14. C-Cell Carcinoma - Higher magnification of Figure 13 (H&E, 102.5x)

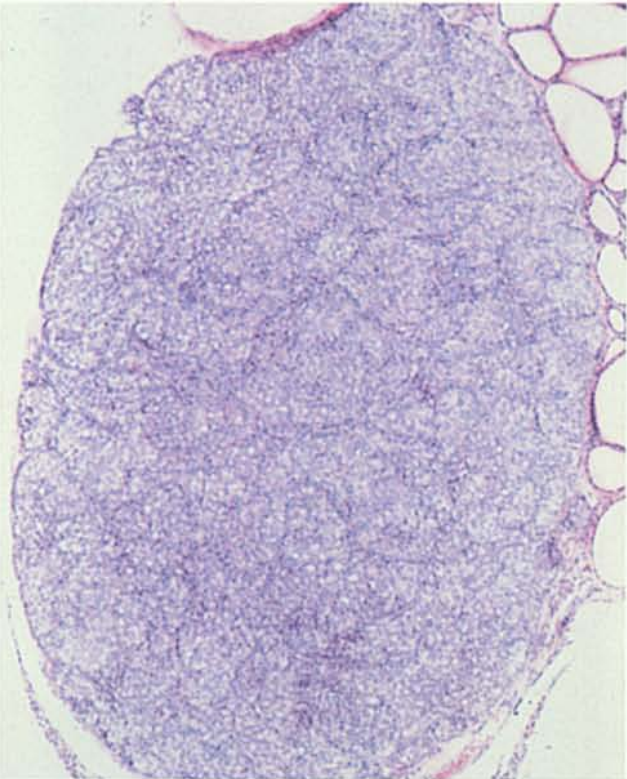


Fig. 15. Parathyroid, Hyperplasia - Diffuse hyperplasia with increased numbers of enlarged pale eosinophilic chief cells. (H&E, 20.5x)

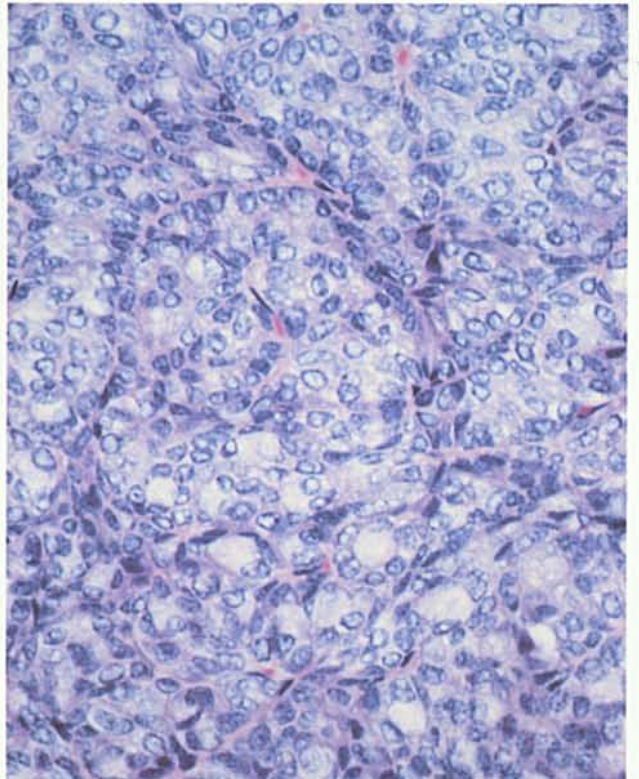


Fig. 16. Parathyroid, Hyperplasia - Higher magnification of Figure 15 (H&E, 205x)

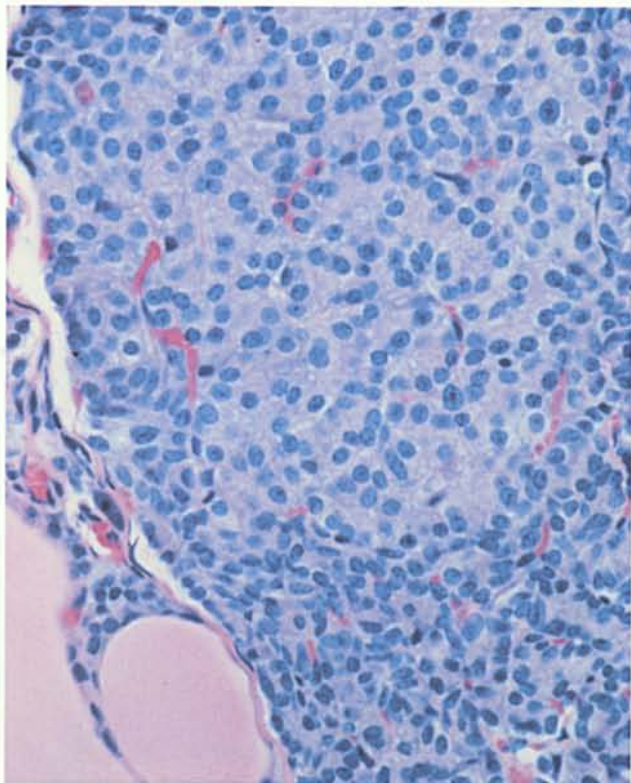


Fig. 17. Parathyroid, Hyperplasia - Focal hyperplasia of chief cells with no compression of surrounding parenchyma. (H&E, 205x)

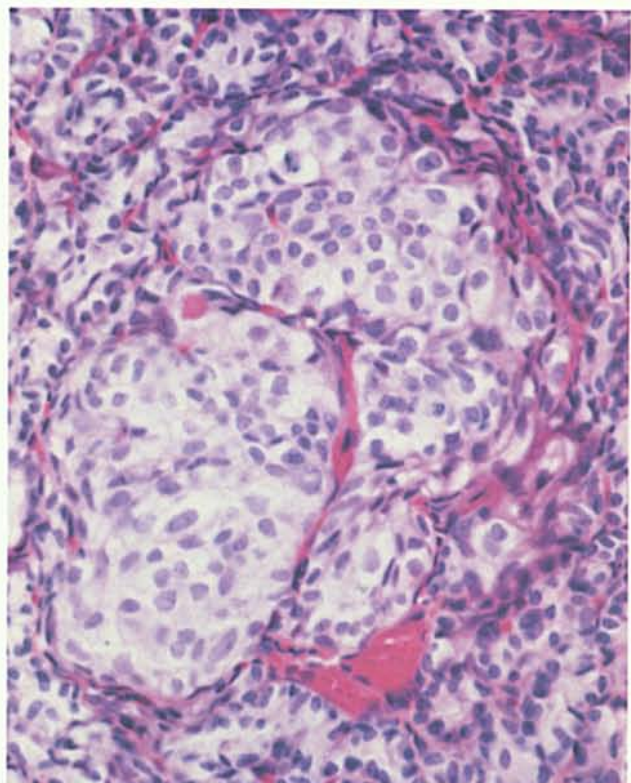


Fig. 18. Parathyroid, Adenoma - Solitary, well-delineated proliferation of chief cells with compression of adjacent tissue. (H&E, 205x)