10 Thyroid Pathology

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10.1 Normal Thyroid

The normal thyroid is a bilobed gland, connected by an isthmus. It is encased by a thin capsule that does not strip easily and contains sizable venous channels. The weight of normal thyroid in the United States ranges from 10 to 20 g. The follicle is the functional unit of the thyroid and averages about 20 μm in diameter [1,2,3,4]. A thyroid lobule consists of 20–40 follicles bound together by a thin sheath of connective tissue and supplied by a lobular artery [3,5]. The thyroid follicles are formed by a single layer of low cuboidal epithelium. The nucleus of the follicular cell is round to ovoid in shape; it is usually centrally placed with an inconspicuous nucleolus. The follicle is enveloped by a basal lamina and is surrounded by numerous capillaries and lymphatics [5,6]. The follicular lumen contains colloid, partly composed of thyroglobulin, which is evenly applied to the luminal cell borders. Calcium oxalate crystals are common in the colloid of adults.

Electron microscopy demonstrates that the normal flat to low cuboidal follicular cells interdigitate and overlap one another, and that they are intimately related to the capillaries that surround the follicle; microvilli on the apical surface are numerous near the cellular margins [6,7].

C cells are intrafollicular and are seen next to the follicular cells and within the basal lamina that surrounds each follicle of the normal gland. C cells are most numerous in the central portions of the middle and upper thirds of the thyroid lobes [3]. They are believed to originate from the C cells that arise from the neural crest and migrate with the ultimobranchial body into the thyroid. C cells are typically more numerous in thyroids of infants as compared to adult glands [8,9]. They are polygonal to spindle shaped, have "light" or low density, cytoplasm, and contain numerous membrane-bound cytoplasmic granules containing calcitonin. A small number of C cells (or cells similar to them) contain somatostatin and can increase in number in some patients [10–13].

C cell aggregates can be sizeable (hyperplastic) in some adults without any known endocrinologic

abnormality [14]. C cell hyperplasia is defined as consisting of more than 40 C cells/cm² and the presence of at least three low-power microscopic fields containing more than 50 C cells [15]. The small solid cell nests of ovoid to spindled epidermoid cells in thyroid are also considered to be of ultimobranchial origin [15]. Typically, the nests have about the same distribution in the thyroid lobes as the C cells [16,17]. The term "mixed follicles" [18] applies to follicles which are lined by follicular cells and epidermoid cells (and sometimes C cells) and contain both colloid and mucoid material. The ultimobranchial structures probably also give rise to a small proportion of normal thyroid follicles [18].

Oxyphil cells (oncocytes, Askanazy cells, Hürthle cells) are altered/metaplastic follicular cells; they are enlarged, have granular eosinophilic cytoplasm, and have large, hyperchromatic, or bizarre nuclei [19]. The cytoplasm is filled with enlarged mitochondria. They are common in longstanding Graves' disease, autoimmune thyroiditis, thyroids affected by radiation, follicular-derived neoplasms, and some adenomatous nodules [19–21].

Small aggregates of lymphoid cells in the thyroid stroma can be seen in normal thyroid gland [22]. Also present in the interstitial tissue are antigen-presenting dendritic cells; these are sparse in the normal gland but are increased in autoimmune thyroid disease [23,24].

10.2 Developmental Variations

The thyroglossal tract extends in the midline from the foramen cecum at the base of the tongue to the isthmus of the normal gland [25]. The tract consists of connective tissue, the thyroglossal duct, lymphoid tissue, and thyroid follicles; it is attached to and may extend through the center of the hyoid bone and is intimately related to the surrounding skeletal muscle. Thyroid tissue may persist at the base of the tongue and in some patients may be the only thyroid present [25,26]. The thyroglossal duct is typically lined by ciliated pseudostratified epithelium. If the duct is traumatized or infected, the epithelium may undergo alteration to transitional or squamous type, or maybe totally be replaced by fibrous tissue. Foreign body reaction and chronic inflammation may be conspicuous. If fluid accumulates in part of the thyroglossal duct, a thyroglossal cyst may develop [3,27,28].

Any type of diffuse thyroid disease can involve lingual thyroid and the thyroid tissue along the thyroglossal tract [28–30]. In rare instances portions of thyroglossal duct are included within the thyroid gland proper and, rarely, can serve as the origin of an intrathyroidal cyst [25]. Parathyroid glands, thymic tissue, small collections of cartilage, and glands lined by ciliated cells may be seen in normal thyroids, presumably related to defective development of the branchial pouches [31–33].

Because of the intimate relationship that exists in the embryo between the immature thyroid tissue and the adjacent developing skeletal muscle, strips of striated muscle are occasionally included within the thyroid [34–36].

Thyroid tissue can be found in close proximity or within the perithyroidal skeletal muscle. Such collections of thyroid tissue are particularly prominent when the gland is hyperplastic or is affected by chronic lymphocytic thyroiditis; these should not be confused with carcinoma [34,37].

Groups of thyroid follicles in lateral cervical lymph nodes always represent metastatic carcinoma (papillary carcinoma) [34,37,38]. A few experienced pathologists state normal thyroid follicles rarely occur in cervical lymph nodes [39]. Hence normal thyroid tissue lying only within the capsule of a midline node may represent an embryologic remnant and not metastatic cancer [39,40].

10.3 Goiter

Goiter is a diffuse or nodular enlargement of the gland usually resulting from a benign process or a process of unknown origin [41–43]. When there is a deficiency of circulating thyroid hormone because of inborn errors of metabolism, iodine deficiency, or goitrogenic agents, and if the hypothalamic-pituitary axis is intact, production of thyroid-stimulating hormone (TSH; thyrotropin) is increased; consequently, cellular activity and increased glandular activity and glandular mass result in an attempt to achieve the euthyroid state [43–45].

Worldwide, the most common cause for a deficient output of thyroid hormone is an inadequate amount of iodine in the diet, leading to iodine-deficiency goiter (endemic goiter) [46,47]. Other causes of hyperplasia include inborn errors of thyroid metabolism (dyshormonogenetic goiter) [48,49], dietary goitrogens, and goitrogenic drugs and chemicals [50–53].

The pathologic changes of simple non-toxic goiter include one or more of the following: (1) hyperplasia, (2) colloid accumulation, and (3) nodularity [41,54,55]. Hyperplasia represents the response of the thyroid follicular cells to TSH, other growth factors, or to circulating stimulatory antibodies [34,55,56]. The hyperplasia may compensate for thyroid hormonal

deficiency, but in some cases, even severe hyperplasia does not lead to sufficient hormonal output to avoid development of hypothyroidism.

If the deficiency of thyroid hormone occurs at birth or early in life, cretinism or juvenile myxedema may result, even though the gland is enlarged and hyperplastic; this is especially likely when an inborn error of thyroidal metabolism is present [57,58]. A hyperplastic gland is diffusely enlarged, and not nodular [34,41,56].

Thyroid follicles are collapsed and contain only scanty colloid. The follicular cells are enlarged and columnar in shape with nuclear enlargement, hyperchromasia, and even pleomorphism. When the hyperplastic stage is extreme and prolonged, there may be confusion with carcinoma because of the degree of cellularity and the presence of enlarged cells. Because of follicular collapse and epithelial hyperplasia and hypertrophy, papillary formation can occur [59]. This pattern occurs most often in untreated dyshormonogenetic goiter [48]. The recognition of the benign nature of this process is possible because of its diffuse nature [59], unlike carcinoma, in which the tumors grow as localized groups of abnormal cells with a background of non-neoplastic parenchyma.

Thyroid follicles may not remain in a state of continuous hyperplasia but instead undergo a process called involution, with the hyperplastic follicles reaccumulating colloid. The epithelium becomes low cuboidal or flattened and resembles that of the normal gland. The gland is diffusely enlarged, soft, and has a glistening cut surface because of the excess of stored colloid. In addition to large follicles filled with colloid, there are foci in the gland where hyperplasia is still evident (Fig. 10.1). This phase of non-toxic goiter is often termed colloid goiter [60,61].

Patients with long-standing thyroid disorders associated with deficiency of circulating thyroid hormone typically develop nodular goiters that result from overdistention of some involuted follicles, and persistence of the zones of epithelial hyperplasia. The new follicles form nodules and may be heterogeneous in their appearance, in their capacity for growth and function, and in their responsiveness to TSH. The vascular network is altered through the elongation and distortion of vessels leading to hemorrhage, necrosis, inflammation, and fibrosis. These localized degenerative and reparative changes produce some nodules that are poorly circumscribed, and others that are well demarcated and resemble true adenomas (adenomatous goiter) [62,63]. Because the nodules distort vascular supply to some areas of the gland, some zones will contain larger than normal amounts of TSH and/or iodide and others will have relative

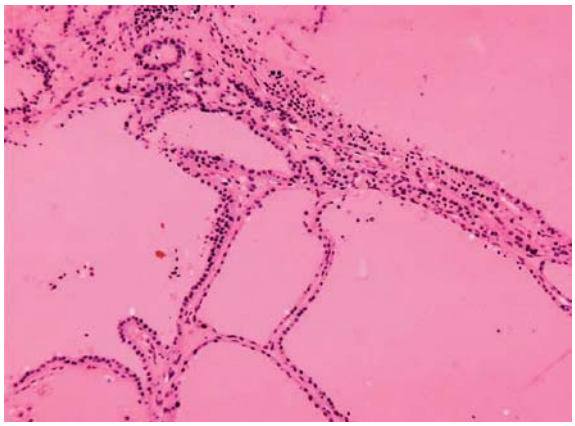

Fig. 10.1 Thyroid follicles lined by low cuboidal epithelium and expanded by thin colloid consistent with colloid goiter

TSH and/or iodide deficiency. Growth of goiters therefore may be related to focally excess stimulation by TSH, stimulation by growth factors, focally abnormal iodide concentration, growth-promoting thyroid antibodies, and poorly understood intrathyroidal factors [47].

Nodular goiter is essentially a process involving the entire gland, but the nodularity may be asymmetric, and individual nodules within the same gland may vary greatly in size. If one nodule is much larger or more prominent than the others (dominant nodule), distinguishing it from a true neoplasm (such as adenoma) may not be possible [37,63]. Several studies have shown that about 70% of dominant nodules in nodular goiter are indeed clonal proliferations [64,65]. The formation of cysts, hemorrhage, fibrosis, and calcification further complicates the assessment of the gland [34,37].

The heterogeneity of the generations of replicating follicular cells, in response to outside stimuli, functional capacity, and rate of growth, forms groups of cells that are hyperfunctional or autonomous, or both. These form "hot" nodules that may cause hyperthyroidism (Plummer's disease) [66].

10.3.1 Graves' Disease

This disorder is also termed diffuse toxic goiter; it is characterized by diffuse enlargement of the thyroid up to several times normal size. The capsule is smooth and the gland is hyperemic. The cut surfaces are fleshy and lack normal translucence because of loss of colloid. If the patient is untreated, the microscopic appearance shows cellular hypertrophy and hyperplasia [34,67]. The follicular cells are tall columnar and are arranged into papillary formations that extend into

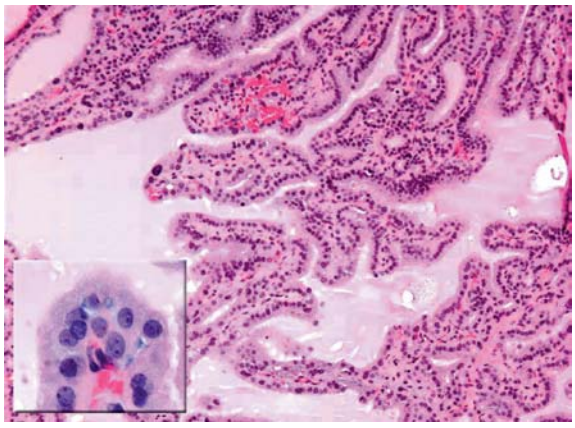

Fig. 10.2 Graves' disease, papillary hyperplasia. Cells lining the papillae show eosinophilic cytoplasm and round nuclei with even chromatin pattern (*inset*)

the lumina of the follicles (Fig. 10.2). Blood vessels are congested. At the ultrastructural level, microvilli are increased in number and elongated, the Golgi apparatus and endoplasmic reticulum are enlarged, and mitochondria are numerous [56,67]. Lymphoid infiltrates are seen between the follicles, ranging from minimal to extensive. T cells predominate among the epithelial cells (cytotoxic suppressor cells) and in the interstitial tissue (helper inducer cells) where there are no lymphoid follicles [68]. B cells are numerous in the lymphoid follicles. Class II major histocompatibility complex antigens are expressed on the epithelial cells, and these epithelial cells induce the proliferation of T cells, helping to perpetuate the process [68–71].

Lymphoid hyperplasia may occur elsewhere in the body: thymus, lymph nodes, and spleen [72,73].

Because nearly all patients now receive antithyroid medication before surgery, the glands can display varying degrees of involution. In some cases they appear almost normal except for numerous large follicles filled with colloid. A few papillae may remain. The hyperemia is notably decreased, especially if there has been preoperative administration of iodide [63]. If the patient has only been treated for symptoms, i.e., with beta-blockers, the histology of the gland resembles that of the untreated state [74,75].

If hyperplasia continues for many months or several years, oxyphilic/oncocytic metaplasia of the cells begins to occur, the amount of stroma increases in an irregular fashion, and nodularity develops, just as in euthyroid goiter. If the process subsides spontaneously or because of the maintenance on antithyroid medication, the involution may be remarkably complete or irregular (with some foci of hyperplasia evident) [74,75].

In some patients the lymphocytic infiltration is very prominent and resembles the gland affected by chronic lymphocytic thyroiditis [34].

10.3.2 Dyshormonogenetic Goiter

When an inborn error of thyroid metabolism exists, and a sufficient amount of circulating thyroid hormone is not available, the normal physiologic response of the pituitary to increase TSH causes a larger, more active thyroid that may or may not be able to produce enough hormones to reach a euthyroid state. The prolonged and marked TSH stimulation leads to an enlarged and nodular thyroid; microscopically there is enlargement of follicular cells, virtual absence of colloid, and increased stroma [49,76].

Large follicular cells with bizarre, hyperchromatic nuclei may be numerous. The enlarged gland, the bizarre cells, and the cellular nodules have at times been mistaken for carcinoma [48] (Fig. 10.3). Cancer can occur in a dyshormonogenetic goiter, but it is very rare [48,77].

10.3.3 Iatrogenic and Related Hyperplasias

Chronic ingestion of excess iodide, for whatever reason, occasionally leads to diffuse hyperplasia. Small nodules with papillary formations may be numerous. Infiltration of lymphocytes may occur [78].

About 3% of patients given lithium salts for a prolonged period develop goiter or hypothyroidism, or both. Patients so treated have been reported to have diffuse hyperplasia with considerable cellular and nuclear pleomorphism [79].

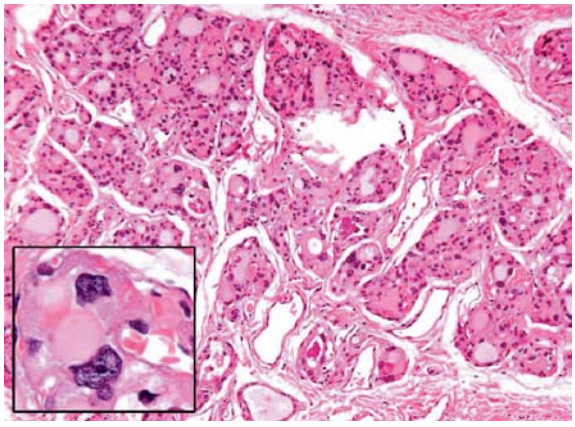

Fig. 10.3 Dyshormonogenetic goiter. Variably sized aggregates of follicular cells and enlarged pleomorphic nuclei (*inset*)

Bromide ingestion may lead to hypothyroidism because of loss of iodide from the gland. This leads to hyperplastic C cells, foci of papillary proliferation, and loss of colloid [80].

10.4 The Thyroiditides

Although occasionally presenting as nodules or asymmetric enlargement of the gland, thyroiditis commonly involves the thyroid diffusely.

10.4.1 Acute Thyroiditis

Acute thyroiditis is rare and is almost always due to infection, although acute thyroiditis may be encountered in the thyroid shortly following radiation exposure [81,82]. The disease is most commonly encountered in malnourished children, elderly debilitated adults, immunocompromised individuals, or in otherwise healthy patients following trauma to the neck [81,83]. Most patients present with painful enlargement of the gland. Microscopically acute inflammation with microabscess formation is present. Microorganisms may be seen. A variety of organisms cause thyroiditis including bacteria, fungi, and viruses [84].

10.4.2 Granulomatous Thyroiditis

Granulomatous subacute thyroiditis, also referred to as non-suppurative thyroiditis or de Quervain's disease, is a rare entity that usually presents in women and has been associated with HLA Bw35 [85]. The changes seen in the gland are most likely due to the response of the thyroid to systemic viral infection [86–88]; some authors suggest that it represents actual viral infection of the gland. Most patients with subacute thyroiditis recover without any permanent damage to the thyroid. However, some studies have reported end stage hypothyroidism in 5–9% of patients [89]. Microscopically, early in the disease, there is loss of the follicular epithelium and colloid depletion. The inflammatory response, composed initially of polymorphonuclear leukocytes and even microabscesses, progresses until lymphocytes, plasma cells, and histiocytes become the major inflammatory cells. A rim of histiocytes and giant cells replaces the follicular epithelium. A central fibrotic reaction occurs [90]. Recovery is associated with regeneration of follicles from the viable edges of the involved areas [91].

10.4.3 Palpation Thyroiditis

Palpation thyroiditis (multifocal granulomatous folliculitis) is found in 85–95% of surgically resected thyroids, and probably represents the thyroid's response to minor trauma. The histologic features of this lesion include multiple isolated follicles or small groups of follicles that show partial or circumferential loss of epithelium and replacement of the lost epithelium by inflammatory cells, predominantly macrophages [92,93].

10.4.4 Autoimmune Thyroiditis

Common synonyms for autoimmune thyroiditis include Hashimoto's thyroiditis, lymphocytic thyroiditis, and struma lymphomatosa [94]. The disorder, most common in women, encompasses a spectrum of clinical and pathologic changes, ranging from an absence of symptoms of thyroid dysfunction to hypothyroidism and rarely, hyperthyroidism, from a large goiter to an atrophic gland, and from scattered clusters of infiltrating lymphocytes to extensive chronic inflammation and scarring with almost complete loss of follicular epithelium [94,95].

Various circulating antithyroid antibodies and other immune phenomena occur, including in situ immune complex deposition and basement membrane changes in the gland and expression of major histocompatibility complex antigens on the thyroid cells [96,97]. The thyroiditis may be found in the same families in which idiopathic hypothyroidism and Graves' disease are common. It may follow typical Graves' disease [98].

The hyperthyroid variant of autoimmune thyroiditis is closely related to Graves' disease and may be almost identical in its gross and microscopic appearance to the latter condition, suggesting that this variant may indeed be Graves' disease [99].

The presence of lymphoid cells in the substance of the thyroid parenchyma probably reflects an abnormal immunologic state. However, the interrelationships among classic chronic thyroiditis, its variants, and "non-specific" thyroiditis are problematic [34]. The morphologic and immunopathologic overlap between non-specific lymphocytic thyroiditis and Hashimoto's disease suggest that they represent a spectrum of autoimmune injury [34,94,100].

In Hashimoto's thyroiditis the gland is firm and symmetrically enlarged weighing from 25 to 250 g [94]. The thyroid has a tan yellow appearance attributed to the abundant lymphoid tissue. The thyroid

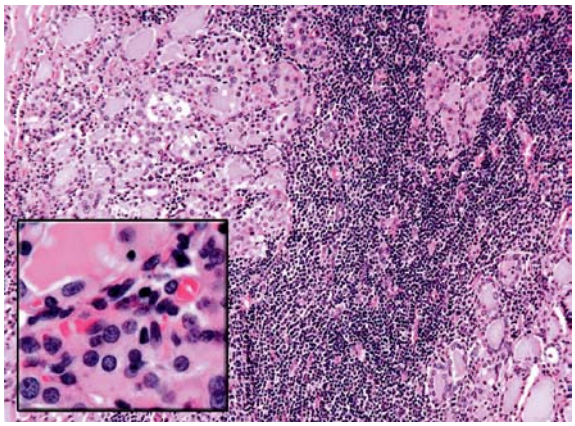

Fig. 10.4 Chronic lymphocytic thyroiditis (Hashimoto's thyroiditis). Oncocytic follicular cells (*inset* showing high power) arranged in nodular pattern with a concomitant lymphocytic infiltrate

follicles are small and atrophic. Colloid appears dense or may be absent. Follicular cells are metaplastic and include oncocytic (Hürthle cell), clear cell, and squamous types. In the stroma and in atrophic follicles, a lymphoplasmacytic infiltration with well-developed germinal centers is found (Fig. 10.4). Variable degrees of interlobular fibrosis are seen [34,94]. The lymphocytic infiltrate is composed of both T and B cells in an almost 1:1 ratio; this differs from the peripheral blood, which shows T cell predominance [101–103]. T lymphocytes within the thyroid are predominantly suppressor type [104,105], whereas the peripheral blood of these patients contains mostly helper T cells. The B cells are usually of the IgG kappa subclass [103].

Patients with Hashimoto's thyroiditis are at increased risk of neoplasia with the most common malignancy being malignant lymphoma, B cell type [106,107]. In addition, patients with Hashimoto's disease may be prone to the development of plasmacytomas within the gland [107]. A peculiar variant of mucoepidermoid carcinoma known as sclerosing mucoepidermoid carcinoma with eosinophilia has been recognized in patients with Hashimoto's disease [108].

10.4.5 Chronic Lymphocytic Thyroiditis Classification

Mizukami et al. established a new classification of chronic lymphocytic thyroiditis [94]. This classification is useful because it allows one to see that the mere presence of lymphocytes in the thyroid does not indicate autoimmune disease. They basically divided their patients into four groups:

1. *Chronic thyroiditis, oxyphilic.* This group contains patients with classic Hashimoto's disease histology.
2. *Chronic thyroiditis, mixed.* This group shows less of an infiltrate than group 1 with minimal fibrosis. Patients demonstrate either eu-, hyper-, or hypothyroidism.
3. *Chronic thyroiditis, hyperplastic.* This group shows glandular hyperplasia associated with only a small lymphocytic reaction. Most patients are hyperthyroid.
4. *Chronic thyroiditis, focal.* This group shows only a focal lymphocytic reaction and most patients are euthyroid.

10.4.6 Fibrosing Variant of Hashimoto's Thyroiditis

The fibrous or fibrosing variant of Hashimoto's thyroiditis comprises approximately 10–13% of all cases of Hashimoto's disease. Pathologically, the thyroid architecture is destroyed with severe follicular atrophy, dense keloid-like fibrosis, and prominent squamous or epidermoid metaplasia of the follicular epithelium [109,110]. Surgery in this setting can be extremely difficult.

10.4.7 Painless/Silent Thyroiditis

Painless thyroiditis is an autoimmune disease that causes painless enlargement of the thyroid gland along with brief hyperthyroidism followed by hypothyroidism. It can occur in the postpartum period and is termed postpartum thyroiditis [111–113]. Most cases show follicular disruption and lymphocytic infiltration, but stromal fibrous and oxyphilic changes are rare [111].

10.4.8 Focal Non-specific Thyroiditis

Lymphocytic infiltration of the thyroid is found more frequently at autopsy and in surgical specimens since the addition of iodide to the water supplies of the United States about 60 years ago [114,115]. It has been suggested that iodide (iodine) may combine with a protein, act as an antigen, and evoke an immune response localized to the thyroid gland [116]. Postmortem studies indicate an incidence of focal

lymphocytic thyroiditis of about 15–20% in women and rarely in men [114]. These cases show focal aggregates of lymphocytes, occasional germinal center formation, but oncocytes are rarely present. Follicular atrophy is also rare [100].

10.4.9 Riedel's Thyroiditis

Riedel's thyroiditis (Riedel's disease, invasive fibrous thyroiditis, Riedel's struma) has been incorrectly included among the thyroiditides [117]. This is really not a disorder of the thyroid but one that involves the thyroid as well as other structures in the neck or even systemic structures; sclerosing mediastinitis, retroperitoneal fibrosis, pseudotumor of the orbit, and sclerosis of the biliary tract (sclerosing cholangitis) [118–121]. Riedel's disease is an extremely rare entity with an incidence of 0.05% of surgical thyroid diseases and showing a female predominance [122]. Most patients are euthyroid, although hypothyroidism and hyperthyroidism have been reported [117,122].

Descriptions of the thyroid range from stony hard to woody fixed ("ligneous" thyroiditis). Histologically, the involved portions of the gland are destroyed and replaced by keloid-like fibrous tissue associated with lymphocytes and plasma cells [122,123]. The fibrous tissue extends into muscle, nerves, and fat, and entraps blood vessels. In about 25% of cases, the parathyroid glands are also encased [123,124]. There is an associated vasculitis (predominantly a phlebitis) with frequent thrombosis [125].

Quantitative studies of the immunoglobulin-containing cells in fibrous Hashimoto's thyroiditis show that cells containing kappa light chains outnumber lambda-containing cells (64% versus 36%) whereas in Riedel's disease lambda-containing cells comprise >70% of the immunocyte population. In Hashimoto's thyroiditis, IgA cells make up about 15% of the lymphocytes, whereas IgA-containing plasma cells comprise about 45% of the immunocyte population in Riedel's disease. The immunologic evaluation supports the separation of the distinctive Riedel's lesion from other thyroiditides [126].

10.4.10 Combined Riedel's Disease and Hashimoto's Thyroiditis

In rare instances the thyroid gland can show features of both Riedel's disease and Hashimoto's thyroiditis. The histologic picture resembles Riedel's disease, whereas the serology shows thyroglobulin and microsomal antibodies seen in Hashimoto's thyroiditis [127].

10.5 Amiodarone Injury with Thyrotoxicosis

Administration of amiodarone may cause thyrotoxicosis, primarily due to the large quantity of iodine in the drug [78,128]. Tissue changes are usually focal. Groups of follicles contain degenerated follicular cells (with granular or vacuolated cytoplasm); some follicles have lost follicular cells, and there is partial or complete loss of colloid. Zones of fibrosis are evident. The intervening thyroid tissue is normal [129].

10.6 Miscellaneous Disorders

10.6.1 Radiation Effects

Ionizing radiation delivered in small doses to the thyroid glands of infants, children, and adolescents causes a marked increase in the later incidence of benign and malignant neoplasms [130]. Larger doses produce more numerous nodules; many of these nodules are particularly cellular, and some are atypical in their structure and cytologic features, suggesting premalignant characteristics [131]. The cancers that develop after small doses of radiation are mostly papillary carcinomas, are often multicentric or bilateral, and are frequently small [130]. In addition to the nodules and neoplasms that occur, other changes are believed to be more common as well, including focal epithelial hyperplasia (possibly incipient nodules), chronic lymphocytic thyroiditis, oxyphilic metaplasia of follicular cells, and slight fibrosis [132,133].

Large doses of ionizing radiation (e.g., therapeutic radiation for head and neck cancer, or radioiodine therapy) can initially cause vascular injury and follicular cell necrosis. Hemorrhages, edema, and small numbers of the usual inflammatory cells appear. The damaged is healed by scarring and the follicular epithelium can show a mixture of atrophic, hyperplastic, and metaplastic changes [134,135].

10.6.2 Amyloidosis

The thyroid may be involved by primary or secondary amyloidosis. The amyloid deposition may be sufficiently uneven to produce a mass. Such an accumulation must

be differentiated from that occurring in some cases of medullary carcinoma [136,137].

10.6.3 Black Thyroid

Prolonged therapy with tetracycline antibiotics, especially minocycline, may cause the accumulation of sufficient pigment in the follicular cells to produce a dark brown to black gland. Much of the pigment is lipofuscin, but part may be a metabolite of the drug. Rarely, there may be interference with thyroid function [138,139].

10.7 Neoplasms

Thyroid neoplasms demonstrate a variety of morphologic patterns that complicate their pathologic interpretation [140]. All neoplasms that arise from thyroid epithelial cells may have some functional capacities. They may respond to TSH and may even produce excessive amounts of thyroid hormones or, if medullary carcinoma, release abnormal quantities of calcitonin or other hormones [34]. Localization of thyroglobulin or calcitonin by immunohistochemistry aids in the classification of unusual thyroidal tumors and in providing definite identification of metastatic thyroid carcinomas [37].

10.7.1 Benign Neoplasms

10.7.1.1 Adenomas and Adenomatous Nodules

A follicular adenoma or solitary adenomatous or adenomatoid nodule is defined as a benign encapsulated mass of follicles, usually showing a uniform pattern throughout the confined nodule [35,37]. Follicular adenomas with papillary hyperplasia (some of which are functional) should not be classified as papillary adenomas [141], but as papillary hyperplastic nodules [142]. Adenomas are solitary; indeed, if there are multiple nodules in a lobe or a thyroid gland, it is probably more appropriate to diagnose multinodular goiter with adenomatous change (adenomatous hyperplasia). The features that distinguish histologically between adenoma and adenomatous nodules included encapsulation, uniformity of pattern within the adenoma, and compression of the surrounding gland by the adenoma and its capsule (Fig. 10.5) [143].

Descriptive terms that have been used to delineate the patterns seen in follicular adenomas include macrofollicular, simple, microfollicular, fetal, embryonal, and trabecular [35]. However, since these patterns have no clinical importance, it is not necessary to subdivide thyroid adenomas. Relatively common changes found in adenomas include hemorrhage, edema, and fibrosis, especially in the central portions of the tumor [35]. Calcification may be seen. Lesions that have undergone fine-needle aspiration biopsy may show necrosis, increased mitotic activity, and cellular atypia in the area of the needle tract [144].

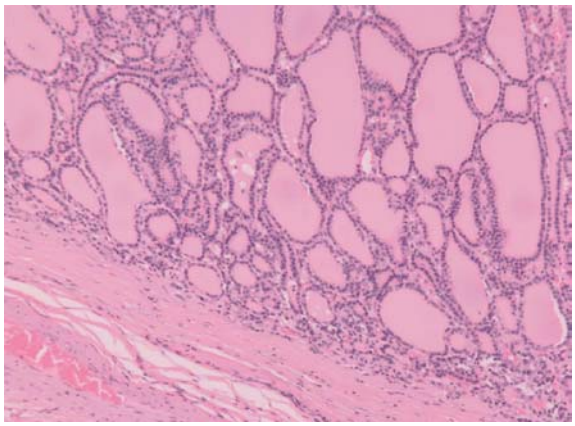

Fig. 10.5 Follicular adenoma. Thinly encapsulated follicular patterned lesion and lack of capsular or vascular invasion

Whether or not some solitary follicular nodules have the biologic potential to become carcinoma is unknown; the findings of aneuploid cell populations in 27% of such lesions suggest that some of these may represent carcinoma in situ [145,146]. The solitary follicular lesion that is removed by lobectomy and when adequately studied shows no evidence of invasion, will neither recur nor metastasize [35]. (Enucleation of follicular adenomas or nodulectomy should be condemned as a surgical procedure and considered suboptimal care. The pathologic evaluation of these lesions requires analysis of the tumor capsule–thyroid interface [143].)

Hyalinizing Trabecular Adenoma/Neoplasm of the Thyroid

The hyalinizing trabecular adenoma is a distinct patterned follicular-derived lesion of the thyroid; i.e., it expresses thyroglobulin, thyroid transcription factor (TTF1) and not calcitonin [147]. Microscopically, these adenomas grow in nests that are surrounded by dense hyaline stroma. The nested histology of the tumor cells is reminiscent of that seen in paragangliomas (thus termed by some authors as paraganglioma-like adenoma of thyroid—PLAT) [148]. The nuclear features of the follicular cells are similar to those seen

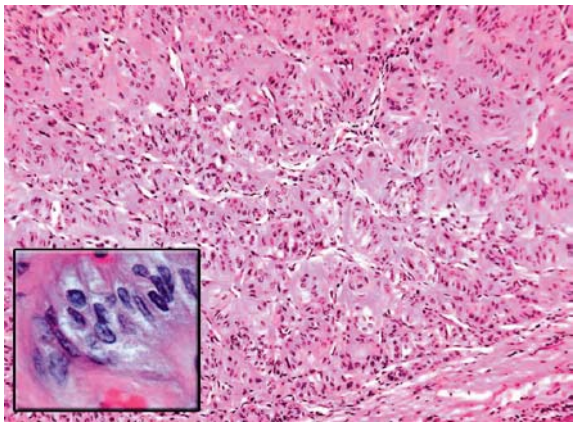

Fig. 10.6 Hyalinizing trabecular neoplasm. Tumor mainly of elongated cells (*inset*) and hyalinized stroma

in papillary carcinoma (Fig. 10.6) [149]. By immunohistochemistry, the cells of hyalinizing trabecular adenoma stain positive for thyroglobulin and cytokeratin 19 and negative for calcitonin, although the presence of other neuroendocrine markers has been described [150].

Some authors have proposed that these adenomas actually represent a variant of papillary carcinoma. This is due to similar nuclear cytology, immunoprofile, and RET oncogene rearrangements in both tumors [151]. However, a benign behavior has so far been described in all cases of hyalinizing trabecular adenoma. Therefore, we believe until metastatic behavior is described in a case of hyalinizing trabecular adenoma with classic histology, these tumors can be designated as hyalinizing trabecular neoplasm as proposed by the World Health Organization [149].

Atypical Follicular Adenoma

The term atypical follicular adenoma includes those follicular tumors that show pathologically disturbing features (spontaneous necrosis, infarction, numerous mitoses, or unusual cellularity), but do not show invasive characteristics on careful examination. The overwhelming majority of the atypical adenomas behave in a benign fashion clinically [152–154].

10.7.2 Malignant Neoplasms

The most common malignant neoplasms of the thyroid origin are the well-differentiated carcinomas of follicular epithelial origin: up to 80% of these are papillary carcinomas [35]. Most non-neoplastic diseases of the thyroid do not seem to be precursors of malignant diseases, with the exception that autoimmune thyroiditis may predispose to malignant lymphoma [37]. Anaplastic carcinomas have often arisen in goitrous thyroids, and careful examination of the resected tissues has frequently demonstrated benign tumors or well-differentiated carcinomas in close association with the anaplastic neoplasm. Such findings have led to suggestions that the benign tumor or low-grade carcinoma can "transform" into the anaplastic carcinoma [155].

10.7.2.1 Papillary Carcinoma

This is the most common malignant tumor of the gland in countries having iodine-sufficient or iodine-excess diets, and comprises about 80% of thyroid malignancies in the United States [156–158]. Papillary thyroid carcinoma (PTC) clinically behaves in an indolent fashion and carries an excellent prognosis (>90% survival at 20 years) [158]. It invades lymphatics leading to multifocal lesions and to regional lymph node metastases [156,158]. Venous invasion rarely occurs and metastases outside the neck are unusual (5–7% of cases) [159].

Papillary thyroid carcinoma can occur at any age and rarely has been diagnosed as a congenital tumor [160]. Most tumors are diagnosed in patients in the third and fifth decades. Women are affected more than men in ratios of 2:1 to 4:1 [161].

Etiologic Factors

Etiologic factors for PTC are not well established; various cellular and genetic mechanisms/targets have been studied in the development of PTC.

Iodide

The addition of iodine to the diet in endemic goiter areas in Europe has been associated with a decreased incidence of follicular cancer and an increase in PTC [162,163].

External Radiation

External radiation probably plays a role in the development of PTC [164,165]. The average time from radiation exposure to tumor development has classically been reported as 20 years; however, development time can be variable [130,165]. The Chernobyl

nuclear accident has induced a great increase in the incidence of PTC in Belarus, Russia, and Ukraine [130]. The increased incidence is seen predominantly in young children. Most reported tumors following this nuclear disaster have been PTC, some of which show aggressive features including extracapsular extension and vascular invasion; however, mortality is extremely low [130,166].

Autoimmune Disease

Many studies indicate that up to one third of PTCs arise in the setting of chronic thyroiditis. Follow-up studies of patients with documented thyroiditis indicate that the tumor that arises much more frequently in these glands is malignant lymphoma, not PTC (see below) [167]. Since papillary cancer and thyroiditis are both common conditions, the possibility of coincidental coexistence is more likely than an etiologic relationship [167,168]. However, loss of heterozygosity for various tumor suppressor genes has been demonstrated in the cytologically atypical areas/nodules in chronic lymphocytic thyroiditis [169]. Thus, a link may exists between chronic lymphocytic thyroiditis and PTC.

Hormonal and Reproductive Factors

Papillary thyroid carcinoma is more common in women than men. Some studies have suggested the role of various hormonal factors in the development of PTC; these include increased parity, late age at the onset of first pregnancy, fertility problems, and oral contraceptives [170]. However, studies of steroid hormone receptors have been disappointing since about 50% of normal thyroid, and benign and malignant nodules can contain estrogen and/or progesterone receptors and smaller numbers of androgen receptors. No correlation with age or gender has been identified [171].

Genetic Syndromes

Papillary carcinomas have been described in patients with familial adenomatous polyposis coli (FAP), Cowden's syndrome, non-polyposis colon cancer syndrome (HNPCC), Peutz Jeghers' syndrome, and ataxia telangiectasia [172–174].

Familial adenomatous polyposis coli is caused by germline mutations of adenomatous polyposis coli (APC) gene. PTC (>95% of cases) occurs in 12% of patients with FAP; all these patients do show germline mutations of the APC gene, however, somatic mutations or loss of heterozygosity for the APC gene are not found in thyroid tumors. Interestingly, a majority of these tumors do show activation of ret/ptc1 in thyroid tumors suggesting a possible association between APC and ret/ptc in the development of this particular subset of familial papillary carcinoma [172–177].

Cowden's syndrome is characterized by formation of hamartomas in several organs and a high risk of developing breast and thyroid cancer. The genetic locus for Cowden's syndrome has been mapped to chromosome 10q23.3 and is also known as PTEN, which is a protein tyrosine phosphatase and exerts its tumor suppressor effects by antagonizing protein tyrosine kinase activity. Interestingly, PTEN mutation or gene deletion is noted in 26% of benign tumors but only in 6.1% of malignant tumors of the thyroid [178,179].

Thyroid/Parathyroid Adenomas

Occasionally, papillary cancers arise in benign nodules or adenomas. It is believed that this is likely to be a random event of location and does not indicate a casual relationship [143]. Several authors have described the association of PTC and parathyroid adenoma and/or hyperplasia [180,181]. Both types of lesions are associated with a history of low-dose external radiation to the neck.

Pathology

The gross appearance of PTC is quite variable. The lesions may appear anywhere within the gland. By definition, clinical papillary carcinomas are >1.0 to 1.5 cm in size often averaging 2–3 cm, although lesions may be quite large. The lesions are firm and usually white in color with an invasive appearance. Tumoral calcification is a common feature. Because of extensive sclerosis, the tumor may grossly resemble a scar. In addition, cyst formation may be observed [34,35,156].

Microscopically, PTC displays papillae containing a central core of fibrovascular tissue lined by one or occasionally several layers of cells with crowded/overlapping oval nuclei. The nuclei of papillary cancer have been described as clear, ground glass, empty, or Orphan Annie eyed. These nuclei are larger and more oval than normal follicular nuclei and contain hypodense chromatin. Intranuclear inclusions of

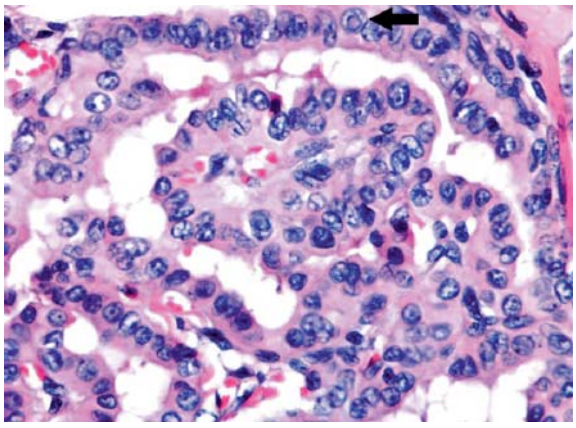

Fig. 10.7 Papillary carcinoma, classic type. Tumor cells arranged in papillary groups and showing chromatin clearing, intranuclear grooves, and inclusions (*arrow*)

cytoplasm are often found. Another characteristic of the papillary cancer nucleus is the nuclear groove (Fig. 10.7) [37,156,157]. Nuclear grooves may be seen in other thyroid lesions including Hashimoto's disease, adenomatous hyperplasia, and diffuse hyperplasia as well as in follicular adenomas (particularly hyalinizing trabecular neoplasm) [182]. Hence, the mere presence of nuclear grooves is not diagnostic for papillary carcinoma.

Psammoma bodies are lamellated round to oval structures that represent the "ghosts" of dead papillae and are formed by focal areas of infarction of the tips of papillae attracting calcium that is deposited upon the dying cells. These are seen within the cores of papillae or in the tumor stroma [35,156]; only rarely are psammoma bodies found in benign conditions in the thyroid [183,184]. Psammoma bodies are found in about 40–50% of cases, but their presence in thyroid tissue indicates that a papillary carcinoma is most likely present somewhere in the gland [35,37]. The finding of psammoma bodies in a cervical lymph node is strong evidence of a papillary cancer in the thyroid [185].

Scattered lymphocytes are common at the invasive edges of the tumor [186,187]. Cyst formation may occur and in fact may be so striking that the diagnosis of PTC is difficult to make particularly if the lesion has metastasized to neck lymph nodes making the distinction clinically from a branchial cleft cyst difficult [34,188,189].

Papillary thyroid carcinoma early in its development invades the glandular lymphatics [34], which accounts for the high incidence of regional node metastases [156]. The tumors can also present multifocally within the same gland [156]. It has been shown by molecular biology techniques that papillary carcinomas are clonal proliferations [190]. In view of these studies it is believed that multifocality of papillary carcinoma must be due to intrathyroidal lymphatic spread rather than multifocal primary tumors [64,190]. Recent RET/PTC and LOH studies have shown that multifocal papillary microcarcinomas can be separate primaries instead of intraglandular spread from one tumor source [191,192].

Venous invasion can be identified in up to 7% of papillary cancers [193]. Whether this finding alone is predictive of a more aggressive behavior is unclear [194,195].

Regional lymph node metastases are extremely common (50% or more) at initial presentation of usual papillary cancer (Fig. 10.8) [158]. Some patients will present with cervical node enlargement and will have no obvious thyroid tumor [196]. Not infrequently the nodal metastasis will involve one node that may be cystic. The histology of the nodal metastases in papillary cancer may appear papillary, mixed, or follicular. This feature does not adversely affect long-term prognosis [156,157]. Hence, attempts at staging of papillary carcinoma may have minimal clinical significance.

Tumor grading is of no use in this tumor since over 95% of these lesions are grade 1 [194]. In some tumors, either in the primary site or in recurrences, areas of poorly differentiated cancer characterized by solid growth of tumor, mitotic activity, and cytologic atypia can be found. Such lesions have a much more guarded prognosis [197]. Anaplastic change in a papillary cancer can occur, although it is uncommon [155].

Distant metastases of papillary carcinoma to lungs, bones, and brain occur in 5–7% of cases [198]. Despite the presence of multiple metastases, however, survival

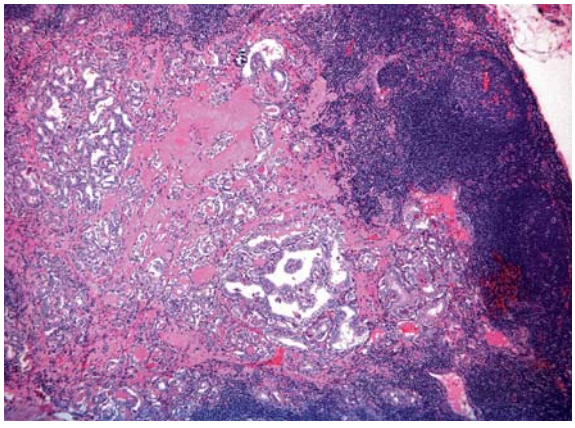

Fig. 10.8 Lymph node with metastatic papillary carcinoma

may still be prolonged, especially if the metastases can be treated with radioiodine [199]. In ordinary papillary carcinoma, death is uncommon [199].

Immunohistochemistry

Immunostaining shows that most papillary cancers express thyroglobulin, TTF1, and not calcitonin [37]. Several reports have been published regarding the use of various immunohistochemical markers that can differentiate papillary carcinoma from other follicular-derived lesions of the thyroid. From an extensive list of these markers the ones that have shown some promise include cytokeratin 19, HBME1, and galectin 3 [200–205]. However, none of these have proven to be specific since all can be expressed in some benign lesions of the thyroid. Therefore, some authors have proposed that diagnosis of PTC by immunohistochemistry should be carried out by using the markers mentioned above in an immunopanel [202,206].

The other markers that have been explored in the diagnosis of PTC include: S100 protein, blood group antigens, estrogen receptors, CD10, CD15, and CD57. The proliferation of markers indicates that no one of them is useful for the daily practice of pathology [207–210].

Flow Cytometry

Although the great majority of papillary thyroid cancers are diploid, the literature suggests up to 20% may show aneuploid or at least non-diploid subpopulations. It has been shown that aneuploid tumors are often associated with a more aggressive clinical course; however, multivariate analysis has not shown that ploidy is an independent prognostic factor [146,157,211].

Molecular Pathology

In the decade since 1995 the literature on thyroid has been focused mainly on the role of various biologic events and genetic determinants in the pathogenesis of various thyroid tumors. Rearrangements of RET gene, known as RET/PTC have been identified in papillary carcinoma of the thyroid [212,213]. The RET protooncogene is normally expressed in cells of neural crest origin and plays a role in kidney and gastrointestinal neuronal development. It is located on chromosome 10q11.2 and cell membrane receptor tyrosine kinase [212,214]. In normal thyroid wild-type RET is only expressed in C cells and not follicular cells. RET/PTC seen in papillary carcinomas occurs due to fusion of the tyrosine kinase domain of RET to the 5′ portion of the various genes. To date more than ten novel types of rearrangements have been described in papillary carcinoma. RET/PTC1 and 3 are the most common forms that occur in sporadic papillary carcinoma. RET/PTC1 is formed by fusion of RET to *H4* and RET/PTC3 occurs due to fusion of RET to *ELE1* gene [214–216].

RET/PTC expression in thyroid follicular cells of transgenic mice leads to development of thyroid tumors with histologic features of papillary thyroid carcinoma [217]. Similarly, transfection of follicular cells in tissue culture by RET/PTC causes the cells to demonstrate nuclear features of papillary carcinoma [218]. The prevalence of RET/PTC in papillary carcinoma varies significantly among various geographic regions; in the United States it ranges from 11% to 43% [216]. In sporadic tumors RET/PTC1 is the most common form of rearrangement (60–70%) followed by RET/PTC3 (20–30%) [216,219]. The other rare forms of RET/PTC rearrangements have been mainly found in radiation-induced papillary carcinomas. Several studies have shown a strong association between radiation-induced papillary carcinoma and expression of RET/PTC; in papillary carcinoma in children affected by the Chernobyl nuclear accident, RET/PTC3 was found to be the commonest form of rearrangement followed by RET/PTC1 [220,221].

Recently it has been shown that RET/PTC expression can also occur in some benign lesions. These include hyalinizing trabecular neoplasm [151], Hashimoto's thyroiditis [222,223], and hyperplastic nodules and follicular adenoma [224].

Several authors have suggested an association between Hashimoto's thyroiditis and PTC; however, others have suggested that this association is most likely incidental since both are common. Recently two independent studies have shown high prevalence of RET/PTC in histologically benign thyroid tissue affected by Hashimoto's thyroiditis; these studies concluded that thyroiditic glands harbor multiple foci of papillary carcinoma that are not identified by histologic examination only [222,223]. However, a more recent study failed to reproduce these results [168].

RET/PTC has been identified in benign thyroid nodules, especially the ones that are seen in patients with a history of external radiation [224]. However, this still remains controversial and needs to be further elucidated by examination of a large cohort of cases.

Activation of the ras oncogene-signaling pathway is considered to be an important mechanism by which human cancer develops. Ras has been shown to regu-

late several pathways that contribute to cellular transformation including the Raf/MEK/ERK pathways. Numerous studies confirm that the Raf/MEK/ERK pathway is a significant contributor to the malignant phenotype associated with deregulated Ras signaling [225,226].

Recently, an activating mutation in the serine/threonine kinase BRAF was described of human PTCs. BRAF-activating mutations in thyroid cancer are almost exclusively the BRAF V600E mutation, and have been found in 29–69% of papillary thyroid cancers, 13% of poorly differentiated cancers, and 10% of anaplastic cancers [226–229]. These data identify that BRAF is an oncogene in human cancer. The high frequency of BRAF mutations in thyroid cancer suggests that inhibition of BRAF activity may represent an important new strategy in the treatment of patients with thyroid cancer.

Prognostic Factors

Poor prognostic factors in papillary carcinoma include older age at diagnosis, male sex, large tumor size, and extrathyroidal growth [158,199]. Pathologic variables associated with a more guarded prognosis include less differentiated or solid areas, vascular invasion, and aneuploid cell population [194]. Some authors have found varying prognostic factors in males and females. In men, age and presence of gross lymph node metastases were important, while in females age, presence of gross lymph node metastases, tumor size, and the number of structures adhered to the gland were important [199,230].

Some studies have shown that RET/PTC expression in papillary carcinoma can be associated with aggressive biologic behavior; conversely, others have reported that its expression is more commonly seen in slow growing and clinically indolent tumors [231,232]. It is also suggested that different rearrangements of RET/PTC are associated with different biologic behavior. Nikiforov et al. found a significant difference in local recurrence and distant metastases between tumor with RET/PTC1 and RET/PTC3 expression [216]. Cetta et al. reported similar findings [233]. Besides RET/PTC, several other biologic markers have been suggested as prognostic predictors in papillary carcinoma; these include p53, Ki67, cell cycle proteins, proliferating cell nuclear antigen (PCNA), bcl2, cathepsin D, and topoisomerase II [234–238].

Subtypes of Papillary Carcinoma

Papillary Microcarcinoma (Occult Papillary Carcinoma)

According to the WHO, papillary microcarcinoma is defined as tumor measuring 1 cm or less; however, some experts have also defined tumors measuring up to 1.5 cm as microcarcinomas (Fig. 10.9) [239,240]. These lesions are quite common as incidental findings at autopsy or in thyroidectomy for benign disease or in completion thyroidectomies in patients with a history of carcinoma involving the opposite thyroid lobe [241]. The incidence of these lesions has varied significantly with the study, but papillary microcarcinoma has been reported in up to 36% of carefully sectioned thyroid specimens [241]. Lymph node metastases from papillary microcarcinoma can occur; metastases from lesions less than 0.5 cm have been reported [240,241]. Distant metastases, although very rare, are also documented [242]. Histologically, the tumors may be totally follicular or show papillary areas as well. Sclerosis may be prominent; the lesions infiltrate the surrounding thyroid [34]. A familial form of papillary microcarcinoma has been recognized; these tumors are characterized by multifocality with increase tendency toward vascular and lymphatic invasion, distant metastasis, and even death [243,244]. It is important to recognize that the incidentally found microcarcinoma confined within the thyroid is probably of no clinical importance and should not be overtreated.

Follicular Variant of Papillary Cancer

The follicular variant of papillary carcinoma is a distinctive papillary carcinoma variant that shows follic-

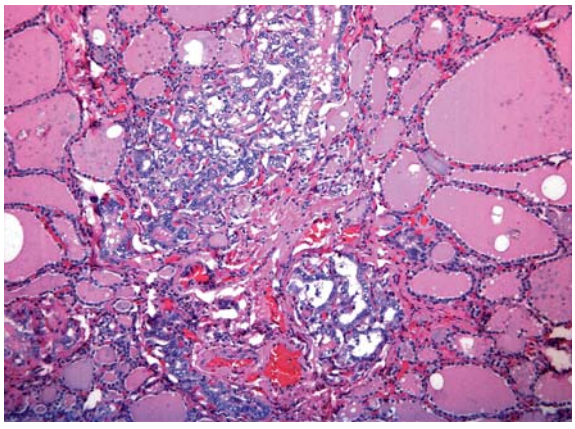

Fig. 10.9 Papillary microcarcinoma

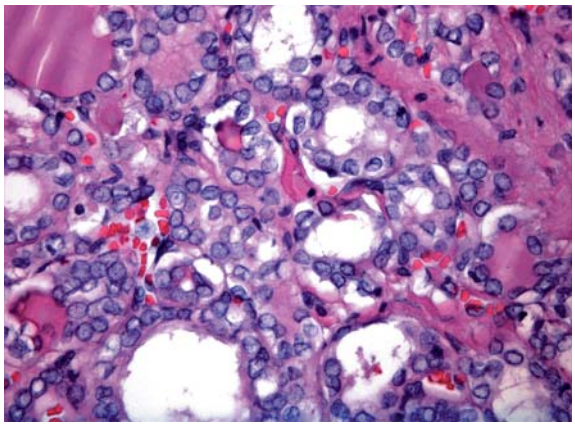

Fig. 10.10 Follicular variant of papillary carcinoma. Variably sized follicles lined by cells showing nuclear features of papillary carcinoma

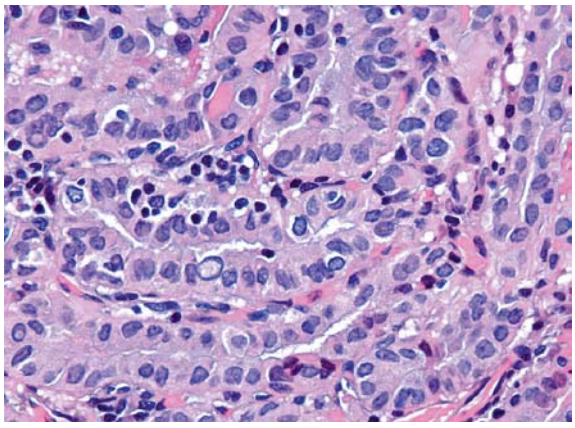

Fig. 10.11 Tall cell variant of papillary carcinoma. Enlarged tumor cells with oncocytic cytoplasm and nuclear features of papillary carcinoma

ular growth pattern and diagnostic nuclear features of papillary carcinoma (Fig. 10.10) [245,246]. The incidence of this variant is difficult to determine since in the past some of these lesions have been classified as follicular carcinomas or adenomas [247]. Grossly and histologically, the tumor may appear encapsulated [248]. The prognosis of the follicular variant is apparently similar to usual papillary cancer although there may be a greater risk for this variant to metastasize outside the neck and for vascular invasion; regional nodal metastases are less common than in classic papillary cancer [249,250].

Two distinct types of follicular variant are the diffuse and the encapsulated follicular variants. In the diffuse follicular variant, the gland is diffusely replaced by tumor [251]. Lymph node and distant metastases are common in these patients. The prognosis appears to be poor in these patients, although only a handful of cases have been described [252,253].

The encapsulated follicular variant refers to the follicular variant that is characterized by the presence of a capsule around the lesion. These lesions are associated with an excellent prognosis [251]. In some cases the diagnosis of this particular variant of papillary carcinoma can be difficult due to the presence of multifocal rather than diffuse distribution of nuclear features of papillary thyroid carcinoma. Because of this peculiar morphologic presentation, these tumors can be misdiagnosed as adenomatoid nodule or follicular adenoma [143,251]. Some authors have suggested that these tumors be classified as "tumors of undetermined malignant potential" due to their excellent prognosis [254]; however, others have shown that some cases belonging in this category can lead to distant metastasis [249].

Tall Cell Variant

The tall cell variant is an aggressive variant of papillary carcinoma that tends to occur in elderly patients. These tumors are usually large (>6 cm), extend extrathyroidally, and show mitotic activity and vascular invasion more often than usual papillary cancer. The tall cell variant of PTC consists of tumor cells twice as tall as they are wide and shows eosinophilic cytoplasm; because of this these tumors are referred to as the "pink cell" variant of papillary carcinoma (Fig. 10.11) [255,256]. Dedifferentiation to squamous cell carcinoma has been described in the tall cell variant of PTC [257]. The prognosis for this variant is less favorable than for usual papillary cancer, although it is believed that the poor outcome is secondary to the fact that these tumors are often associated with poor prognostic variables such as older age, extrathyroidal spread, necrosis, high mitotic rate, and distant metastases [258–260].

Columnar Cell Variant

The columnar cell variant is a rare form of papillary carcinoma [261]. (Some authors believe it is so unusual a tumor that it deserves its own category and should not be placed in the papillary group. The tumor needs to be distinguished from other papillary carcinomas since this lesion is associated with an extremely poor outcome with most deaths occurring within 5 years of diagnosis. Extrathyroidal extension is common as are distant metastases [261–263]. Encapsulated variants, which may have a better prognosis, have been described [264].

Warthin-like Variant

By light microscopy these tumors resemble "Warthin's tumor" of the salivary gland. These tumors usually arise in a background of lymphocytic thyroiditis and show papillary architecture. Limited follow-up has shown that these tumors in their pure form follow a clinical course similar to conventional papillary carcinoma [265,266].

Diffuse Sclerosis Variant

The diffuse sclerosis variant of papillary carcinoma is rare; it most often affects children and young adults, and may present as bilateral goiter. The tumor permeates the gland outlining the intraglandular lymphatics. The lesions tend to recur in the neck and have a somewhat more serious prognosis than usual childhood papillary cancer. These lesions appear to represent 10% of the papillary carcinomas seen in children exposed to the radioactive iodine released following the Chernobyl accident. While the tumors often show extracapsular extension, distant and nodal metastases, and a decreased disease-free survival when compared to the usual type of papillary carcinoma, mortality is low [267–270].

Solid Variant of Papillary Carcinoma

The solid variant of PTC is most commonly seen in children and has been reported in greater than 30% of patients with papillary carcinoma following the Chernobyl nuclear accident [271,272]. It is important to recognize these lesions as papillary carcinomas and not to classify them as more aggressive tumors such as insular carcinoma (discussed below). The prognosis is controversial with some studies showing outcomes similar to typical papillary carcinoma and other studies showing more aggressive behavior [271,273].

Other Variants of Papillary Carcinoma

Rare variants of papillary cancer in which prognostic data are not well established include the spindle cell variant [274], the clear cell type [275], the oxyphilic (Hürthle cell) variant [275,276], papillary carcinoma with lipomatous stroma [277,278], papillary carcinoma with fasciitis-like stroma [279], and the cribriform variant [280–281]. The last of these is often seen in patients with familial adenomatous polyposis although it may occur as a sporadic tumor. It is overwhelmingly common in women [175,282].

10.7.2.2 Follicular Carcinoma

Follicular carcinoma comprises about 5% of thyroid cancers; however, in iodide-deficient areas, this tumor is more prevalent making up 25–40% of thyroid cancers [283,284]. The true incidence of follicular carcinoma is difficult to determine since the follicular variant of papillary carcinoma may still be placed into this category [247]. Risk factors include iodine deficiency, older age, female gender, and radiation exposure (although the relationship of radiation to follicular carcinoma is far less strong than with papillary cancer) [162,285]. Clinically, follicular carcinoma usually presents as a solitary mass in the thyroid [283].

Follicular carcinoma has a marked propensity for vascular invasion and avoids lymphatics; hence, true embolic lymph node metastases are exceedingly rare. Follicular carcinoma disseminates hematogenously and metastasizes to bone, lungs, brain, and liver [283,286,287].

Patients who have follicular carcinoma that is widely invasive fare poorly [284,288]; however, those individual with encapsulated follicular tumors confined to the thyroid enjoy a prolonged survival (greater than 80% at 10 years) [289–292]. Studies using multivariate analysis have identified age >45, extrathyroidal extension, distant metastases, and tumor size >4 cm as independent prognostic factors in follicular carcinoma [286,291,293]. An extremely significant complication that may occur in patients with follicular cancer is transformation into anaplastic cancer; this may occur de novo in an untreated follicular lesion, or in metastatic foci [294].

The *widely invasive follicular carcinoma* is a tumor that is clinically and surgically recognized as a cancer; the role of the pathologist in its diagnosis is to confirm that it is of thyroid origin and is a follicular neoplasm. Up to 80% of the patients with widely invasive cancers can develop metastases, and a 50% fatality rate for widely invasive tumors compared with only 3% for those with minimal invasion has been reported.

The pathologist can only diagnose the minimally invasive follicular carcinoma by examining well-fixed histologic sections. These lesions are not diagnosable by fine-needle aspiration cytology since the diagnosis requires the demonstration of invasion at the edges of the lesion; therefore, sampling of the center, as in obtaining a cytologic sample, cannot be diagnostic [283–287,295–297].

The *minimally invasive follicular carcinoma* is an encapsulated tumor that grossly resembles a follicular adenoma and only on microscopic examination shows evidence of capsular and/or vascular invasion (Figs. 10.12, 10.13). On microscopic examination, follicular carcinomas most often have a microfollicular pattern and resemble a cellular follicular adenoma. Trabecular or solid patterns are fairly common and often accompany the microfollicular pattern [143,291].

What are the minimum criteria for making this diagnosis? Invasion of the capsule, invasion through the capsule, and invasion into veins in or beyond the capsule represent the diagnostic criteria for carcinoma in a follicular thyroid neoplasm [143,247,291]. The criterion for vascular invasion applies solely and strictly to veins in or beyond the capsule, whereas, the definition of capsular invasion is controversial [143,254]. Some authors require penetration of the capsule to diagnose a follicular tumor as carcinoma, while others need tumor invasion through the capsule into the surrounding normal thyroid [254,292]. Is capsular invasion insufficient for the diagnosis of follicular cancer? Distant metastases have been reported in follicular carcinoma diagnosed only on the basis of capsular and not vascular invasion, however, in some cases, metastases were already present at initial diagnosis [290,298]. The presence of vascular invasion is also indicative of malignancy in a follicular tumor. Invasion of vessels within or beyond the lesional capsule is necessary for a definitive diagnosis of vascular invasion [35]. The lesions with vascular invasion should be separated from the minimally invasive follicular carcinomas that show capsular invasion only, because angioinvasive lesions have a greater probability of recurrence and metastasis [251].

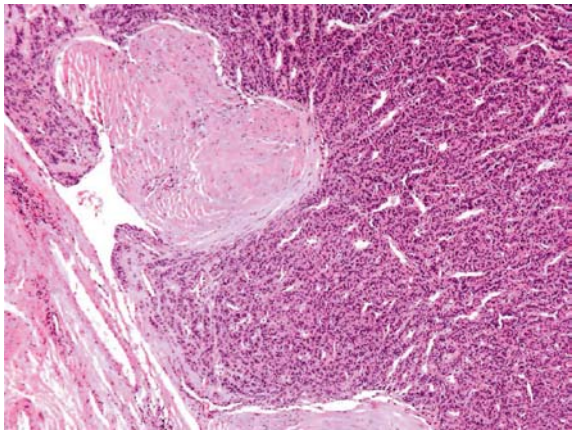

Fig. 10.12 Follicular carcinoma. Thickly encapsulated follicular and solid patterned lesion invading into the capsule in a mushroom-shaped growth

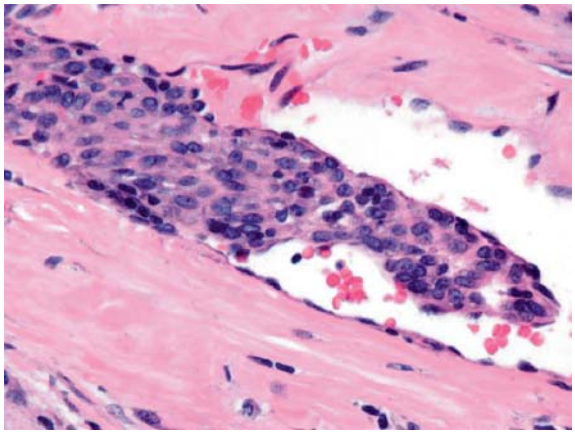

Fig. 10.13 Follicular carcinoma. Tumor embolus within a capsular vessel

In our practice, we use the terms minimally invasive and angioinvasive carcinoma. The former is applied to those cases that show only capsular or transcapsular invasion, while the latter is used for tumors in which vascular invasion is found with or without capsular invasion. As mentioned above, we propose this distinction based on the belief that angioinvasive tumors have a greater propensity toward distant metastasis.

Similar problems exist in evaluating such lesions by frozen section [299,300]. Some authors recommend that intraoperative assessment of such lesions involves the examination of frozen sections from three or four separate areas of the nodule [301]. This wastes resources and rarely gives useful diagnostic information. The surgeon should have removed the lobe involved by the nodule and if it is a follicular carcinoma that is only minimally invasive, the appropriate therapy has probably already been accomplished. Since a only small number of these lesions will show evidence of invasion at the time of permanent section, i.e., the majority of them are benign, and since overdiagnosis is more dangerous for the patient than is the delay in making a definitive diagnosis [299], we discourage frozen section evaluation of these nodules.

None of the ancillary techniques assist in defining benign from malignant follicular tumors. Ultrastructural, morphometric, and flow cytometric analyses have not helped in distinguishing these lesions [145,302]. About 60% of follicular carcinomas will show aneuploid cell populations [145]. Backdahl analyzed 65 follicular thyroid tumors (26 benign and 39 carcinomas). He noted that of the 20 patients with cancer who survived, 19 had diploid tumors, whereas

17 of 19 patients who died of carcinoma had tumors with aneuploid DNA patterns [303].

All follicular carcinomas express thyroglobulin and show a similar cytokeratin profile to normal thyroid parenchyma. Some authors have shown that HBME1 is exclusively expressed in 90–100% of follicular carcinomas and not adenomas. However, others have reported HBME1 expression in adenomatoid nodules and follicular adenomas [204,210,304,305].

Molecular Biology of Follicular Carcinoma

A specific translocation t(2;3) leads to the expression of PAX8 peroxisome proliferator activated receptor gamma (PPAR gamma) chimeric protein; initial studies by Kroll et al. demonstrated that this translocation is specific to follicular carcinoma [306]. However, follow-up studies employing immunohistochemistry and molecular biology have shown that PPAR gamma expression can occur in some cases of follicular adenoma, follicular variant of papillary thyroid carcinoma, and even benign thyroid parenchyma [307,308]. *Ras* mutations are more frequent in follicular carcinoma as compared to follicular adenoma; some authors have found an association between *ras* mutations and clinically aggressive follicular carcinomas [309–311]. Loss of heterozygosity on chromosomes 10q and 3p can be seen in follicular carcinoma suggesting a role of tumor suppressor genes in its pathogenesis [312,313].

Well-differentiated Follicular "Tumors of Undetermined Malignant Potential"

This designation has been recently proposed in thyroid pathology for follicular patterned encapsulated tumors that have been controversial and difficult to diagnose due to: (1) questionable or minimal nuclear features of papillary thyroid carcinoma or (2) questionable or one focus of capsular invasion that is confined to tumor capsule and does not traverse the entire thickness of capsule and lacks any nuclear features of papillary thyroid carcinoma [254].

This terminology may be extremely helpful to pathologists in the diagnoses of certain follicular patterned lesions; however, these terms are proposed on the basis of data that lack complete clinical follow-up. Therefore, clinicians may find it problematic to establish treatment strategies [143].

Oncocytic (Hürthle Cell) Tumors

Hürthle cells are derived from follicular epithelium and are characterized morphologically by large size, distinct cell borders, voluminous granular cytoplasm, large nucleus, and prominent nucleolus. Ultrastructural studies have shown that the cytoplasmic granularity is produced by huge mitochondria filling the cell [314,315]. Hürthle cells can be found in a number of conditions in the thyroid [nodular goiter, non-specific chronic thyroiditis, longstanding hyperthyroidism, and chronic lymphocytic thyroiditis (Hashimoto's disease)] [19].

Perhaps no thyroid neoplasm has elicited more confusion or debate than Hürthle cell (oncocytic) neoplasms. Clinicians and pathologists alike have considered that such tumors do not "follow the rules" for histopathologic diagnosis of malignancy. Some authors cite 80% or more of these lesions as benign, whereas others consider all such lesions malignant [316,317]. Over the decade since 1995, studies from numerous institutions throughout the world have shown that oncocytic or Hürthle cell tumors can be divided into benign and malignant categories by careful adherence to strict pathologic criteria [318,319].

Since most Hürthle cell neoplasms are follicular in pattern, the criterion for distinguishing benign from malignant is the same as for follicular neoplasms, i.e., the identification of capsular and/or vascular invasion [318,319]. However, the pathologic criterion for malignancy is met more frequently for tumors composed of Hürthle cells than for their non-Hürthle counterparts. Thus, whereas 2–3% of solitary encapsulated follicular tumors of the thyroid show invasive characteristics, 30–40% of such lesions showing Hürthle cell cytology will show such features [315,318,320]. In addition, whereas true follicular carcinomas of the thyroid rarely, if ever, metastasize embolically to lymph nodes, about 30% of Hürthle cell carcinomas do [34,321].

Most Hürthle cell neoplasms of the thyroid are solitary mass lesions that show complete or partial encapsulation. They are distinguished from the surrounding thyroid by their distinctive brown to mahogany color [34,35,318]. Rarely, a Hürthle cell neoplasm may undergo spontaneous infarction. Extensive infarction may also be seen following fine-needle aspiration biopsy.

The claim that all Hürthle cell neoplasms should be considered malignant or potentially malignant, especially if 2 cm or greater in size, is no longer considered valid. Many studies from the United States and Europe indicate that benign Hürthle cell neoplasms

exist. Size, nuclear atypia, multinucleation, cellular pleomorphism, mitoses, or histologic pattern of the lesion are not predictive of behavior [315,318,319].

By immunohistochemistry, Hürthle cell lesions are positive for thyroglobulin. Carcinoembryonic antigen (CEA) expression has been described in some, but not all series. Hürthle cell lesions are positive for S100 protein [318,322].

DNA ploidy studies have shown aneuploid DNA patterns in biologically and histologically benign Hürthle tumors of the thyroid. These findings do not indicate malignant behavior, however, about 20–50% of Hürthle cell tumors that are histologically malignant and aneuploid are more aggressive biologically and clinically than diploid Hürthle cell cancers [323].

Molecular Biology of Hürthle Cell Tumors

Hürthle cell tumors are biologically different from other follicular-derived tumors. H-*ras* mutations are more frequent in Hürthle cell carcinoma than follicular carcinoma [324,325], and a high percentage of allelic alterations occur as compared to other follicular-derived tumors. A study by Maximo et al. showed that Hürthle cell tumors display a relatively higher percentage of common deletions of mitochondrial DNA as compared to other follicular-derived tumors. In addition, Hürthle cell tumors also showed germline polymorphisms of ATPase 6 gene, which is required for the maintenance of mitochondrial DNA [326].

Clear Cell Tumors

Clear cell change of the cytoplasm can occur in many follicular-derived lesions of the thyroid, thyroiditis, nodules, and neoplasms [278,327,328]. Of greatest importance is the differentiation of clear cell change in follicular thyroid lesions from clear cell renal cell carcinomas metastatic to the thyroid [329]. Immunostains for thyroglobulin are usually helpful in sorting out this diagnostic problem.

Poorly Differentiated Carcinoma/ Insular Carcinoma

This heterogeneous group of malignant thyroid tumors includes carcinomas that are recognizable as originating from follicular epithelium (often with evidence of coexistent papillary or follicular carcinoma), but that have moderate to high rates of mitotic activity, are composed of solid masses or trabeculae of relatively uniform epithelial cells, have tiny follicles present in varying numbers, may contain regions of acute necrosis, and are more aggressive than the usual well-differentiated carcinomas [197]. Included among these lesions are insular carcinoma, columnar cell, tall cell, and trabecular types of papillary cancer, and "poorly differentiated" carcinoma of Sakamoto [330].

Insular carcinoma or poorly differentiated thyroid carcinoma is a follicular-derived carcinoma with a prognosis between well-differentiated thyroid carcinomas (papillary or follicular) and anaplastic thyroid carcinoma. The term "insular" is used to describe the lesion's histologic growth pattern, which is somewhat "carcinoid-like." The incidence of this tumor appears to vary with differing geographic locations with incidence as high as 5% described in Italy, while the incidence in the United States is much lower [331].

The lesions are often large, gray-white in color, infiltrative, and show extensive necrosis. Microscopically the tumor is composed of small nests of cells that have a neuroendocrine growth pattern. Necrosis, vascular invasion, and mitoses are prominent features. By immunohistochemistry the tumor cells express thyroglobulin and not calcitonin. Insular carcinoma is associated with a worse prognosis than well-differentiated thyroid carcinomas, but is significantly better than anaplastic thyroid carcinoma [331–333]. The extent of the poorly differentiated component in a well-differentiated thyroid tumor can affect the prognosis; tumors with >10% of the poorly differentiated component are associated with frequent regional recurrences, distant metastases, and poor prognosis [334].

10.7.2.3 Anaplastic Thyroid Tumors

Anaplastic carcinomas are a group of high-grade thyroid carcinomas that are usually undifferentiated histologically and advertently have a lethal outcome [155,335]. Synonyms for anaplastic carcinoma include: undifferentiated, dedifferentiated, and sarcomatoid carcinoma. These tumors have represented approximately 10% of thyroid malignancies in older publications [155,336]. The tumor is more commonly seen in elderly females who present with a rapidly enlarging mass that often results in dyspnea. Risk factors are largely unknown but may include history of radiation and iodine deficiency [155]. A precursor well-differentiated thyroid carcinoma (papillary, follicular, or Hürthle cell) may be observed [337].

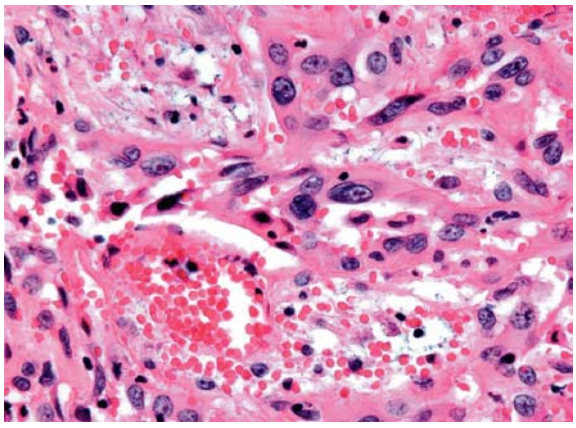

Fig. 10.14 Anaplastic carcinoma. Pleomorphic spindle-shape and epitheloid tumor cells

Grossly, the tumors are large with extensive intrathyroidal and extrathyroidal invasion. Surgical resection is often not performed because of the lesion's extent and diagnosis is commonly made on biopsy. Necrosis, vascular invasion, and mitoses are quite prominent [337]. Histologically, a variety of patterns have been described. The tumors are usually made up of a variety of cell types (Fig. 10.14). Most tumors are composed of giant cells and spindle cells although "squamoid" differentiation is seen in about one third of cases [338]. Osteoclast-like giant cells are a common feature [339]. A "paucicellular" variant of anaplastic carcinoma has been described; it is characterized by dense fibrosis, calcification, and a poor patient outcome [340]. Spindle cell squamous anaplastic carcinoma may be the result of transformation of tall cell papillary carcinoma [257]. Carcinosarcoma of the thyroid has been described [341,342].

Electron microscopic and immunohistologic studies have indicated that almost all anaplastic thyroid tumors are indeed epithelial in nature [338,343]. By immunohistochemistry, anaplastic thyroid carcinomas should be positive for cytokeratin. Thyroglobulin immunostaining is often negative and thyroid transcription factor can be rarely positive in anaplastic carcinoma [343].

10.7.2.4 Thyroid Sarcoma

Sarcomas of the thyroid are rare; fibrosarcomas, leiomyosarcomas, and angiosarcomas have been described [344,345]. Angiosarcoma of thyroid has been most commonly described from the mountainous regions of the world (Alpine regions of Europe, the Andes in South America, and the Himalayas in Asia) [344,346]. Clinically, the affected patients resemble those with anaplastic carcinoma. By gross and histologic examination these tumors resemble angiosarcomas of soft tissue. These tumors generally lack the usual histologic features and exceptional aggressiveness of anaplastic carcinomas, but they are neither typical follicular nor papillary carcinomas.

10.7.2.5 Squamous Cell Carcinoma, Mucoepidermoid Carcinoma, and Intrathyroidal Thymoma-like Neoplasms

Squamous cell carcinoma in thyroid occurs usually in association with papillary or anaplastic carcinoma [257]. Rarely, squamous cell carcinoma appears as an entity independent of any other form of thyroid cancer and behaves in an aggressive fashion with poor prognosis [347]. The major differential diagnosis is metastatic squamous carcinoma, especially from the head and neck, lungs, or esophagus.

Mucoepidermoid carcinoma is a distinctive variant of thyroid carcinoma. It is composed of solid masses of squamoid cells and mucin-producing cells, sometimes forming glands [348]. Some authors consider that this lesion is a variant of papillary carcinoma; all cases show thyroglobulin expression [108,349]. The prognosis of thyroid mucoepidermoid carcinoma is quite good. Lesions may metastasize to regional nodes and rarely distantly. Death from disease is rare [108].

Sclerosing mucoepidermoid carcinoma with eosinophilia is usually seen in a background of lymphocytic thyroiditis and is characterized by tumor cells arranged in small sheets, anastomosing trabeculae, and narrow strands associated with dense fibrosis and numerous eosinophils. While these lesions may metastasize to lymph nodes and show extracapsular spread, vascular invasion, and perineural invasion, death due to disease is uncommon. The tumor cells stain negative for thyroglobulin and calcitonin and positive for cytokeratin [108,350,351].

There is no consensus regarding the origin of these tumors. Some studies have suggested that on the basis of immunoprofile both these tumors have different origins; mucoepidermoid carcinoma shows follicular derivation, and sclerosing mucoepidermoid carcinoma is derived from ultimobranchial body nests/solid cell nests [108].

Rare thyroid tumors composed of spindled epithelial cells arranged in nests, sometimes associated with mucous microcysts, and resembling thymomas (*spindled and epithelial tumor with thymus-like dif-*

ferentiation; SETTLE) have been reported [352,353]. Neoplasms resembling thymic carcinomas have also been described (*carcinoma with thymus-like differentiation; CASTLE*) in thyroid. These lesions may originate from branchial pouch remnants within and adjacent to the thyroid [352,354–356].

10.7.2.6 Medullary Carcinoma

Medullary thyroid carcinoma comprises less than 10% of all thyroid malignancies [357–361]. This tumor is of great diagnostic importance because of its aggressiveness, its close association with multiple endocrine neoplasia syndromes (MEN2A and 2B), and a relationship to a C cell hyperplasia, a probable precursor lesion [362]. While the majority of medullary carcinomas are sporadic, about 10–20% are familial [362]. Since these familial cases have been identified, a gene associated with medullary carcinoma has been identified on chromosome 10 and involves mutations in the RET oncogene [363–365].

Medullary carcinoma can affect patients of any age; most affected individuals are adults with an average age of about 50 years. However, in familial cases, children can be affected; also in these instances the age of diagnosis tends to be younger (mean age about 20 years) [361,366]. Although sporadic medullary carcinomas are seen more commonly in women, familial cases have a slight female to equal sex ratio, since an autosomal dominant mode of inheritance is present [367,368].

Clinically sporadic medullary carcinoma will present with a thyroid nodule that is painless but firm. In up to 50% of cases, obvious nodal metastases will be present at the time of diagnosis. Distant metastases, such as to lung, bone, or liver, may also be noted initially in about 15–25% of cases. When the tumor produces excess hormone other than calcitonin, the presenting symptoms may be related to that hormone hypersecretion [adrenocorticotropic hormone (ACTH), prostaglandin] [369,370].

In the familial lesions there are associated endocrine and/or neuroendocrine lesions. Sipple's syndrome [multiple endocrine neoplasia (MEN) type 2A] [371] consists of medullary thyroid cancer and C cell hyperplasia, adrenal pheochromocytoma and adrenal medullary hyperplasia, and parathyroid hyperplasia [372]. Studies have shown that the gene responsible for familial medullary carcinoma is RET [373,374]; mutations in RET (different from the RET translocation in papillary carcinoma) are found in the tumors and the germline of patients with familial medullary carcinomas and the MEN type 2 syndromes [373–375]. Mutations in specific codons have been correlated with clinical behavior and symptomatology in some families [374]. MEN type 2B consists of medullary thyroid carcinoma and C cell hyperplasia, pheochromocytoma and adrenal medullary hyperplasia, mucosal neuromas, gastrointestinal ganglioneuromas, and musculoskeletal abnormalities [376–379]. These patients may have familial disease (over 50% do), and some cases arise apparently as spontaneous mutations. These patients have biologically aggressive medullary carcinoma and may succumb to metastases at an early age. MEN2B shows similarity to von Recklinghausen's disease since in neurofibromatosis similar lesions are found in the gastrointestinal tract, and pheochromocytomas are common [378,379]. Nerve growth factor has been identified in some medullary carcinomas of these patients; it has been postulated that this product of the tumor may be responsible for the neural lesions seen in the MEN type 2B patients [380]. However, the neural lesions often precede by many years the development of medullary cancer. In MEN type 2B, the tumors and germline mutations in RET are found on codon 918—an intracellular focus of the RET oncogene [381,382].

Medullary carcinoma is usually located in the area of highest C cell concentration, i.e., the lateral upper two thirds of the gland. In familial cases, multiple small nodules may be detected grossly and, rarely, lesions may be found in the isthmus. The tumors range in size from barely visible to several centimeters. Many medullary carcinomas are grossly circumscribed but some will show infiltrative borders. The typical medullary carcinoma may be microscopically circumscribed or more likely will be infiltrating into the surrounding thyroid. The pattern of growth is of tumor cells arranged in nests separated by varying amounts of stroma. The tumor nests are composed of round, oval, or spindle-shaped cells; often there is isolated cellular pleomorphism or even multinucleated cells (Fig. 10.15) [383,384]. The tumor stroma characteristically contains amyloid although this is not necessary for the diagnosis as about 25% of medullary carcinomas do not contain amyloid (Fig. 10.15) [361,385,386]. The amyloid is most likely derived from procalcitonin and indeed immunohistochemical stains for calcitonin often stain the amyloid [37,386]. Calcifications in areas of amyloid deposition are characteristically present. The tumors commonly invade lymphatics and veins [384].

Several variants of medullary carcinoma on the basis of growth pattern have been described. These include: papillary variant, follicular variant, encap-

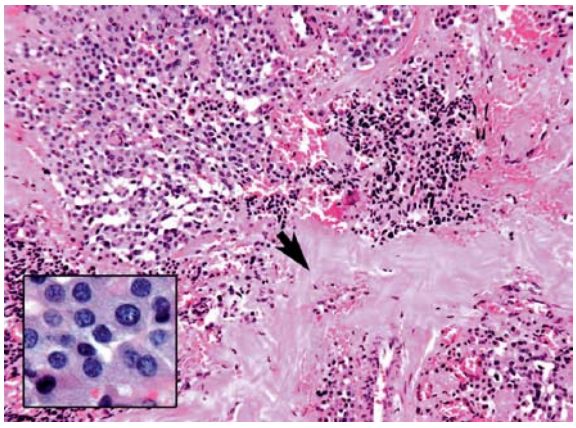

Fig. 10.15 Medullary carcinoma. Tumor cells arranged in nests and round nuclei with finely granular chromatin (*inset*) in a background of stroma and amyloid (*arrow*)

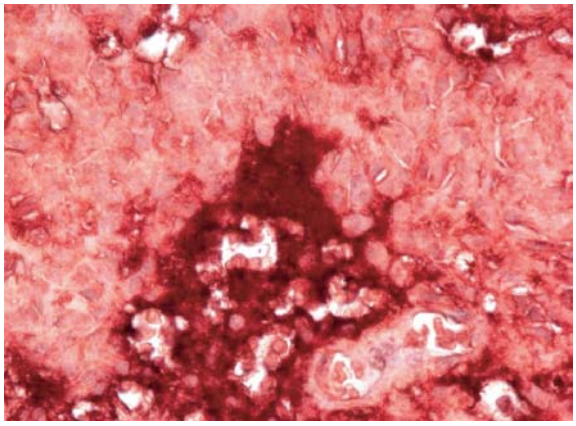

Fig. 10.16 Medullary carcinoma showing positive immunostaining with calcitonin antibody. The tumor is staining dark, and light staining is seen in the background amyloid

sulated variant, small cell variant, giant cell variant, oncocytic variant, and clear cell variant [389–391].

By immunohistochemistry, the majority of medullary carcinomas express low molecular weight cytokeratin, calcitonin (Fig. 10.16), calcitonin gene-related peptide, and thyroid transcription factor (TTF1). In addition, many tumors express CEA, which may also be elevated in the serum [392–394]. A variety of other peptides may be found in tumor cells including somatostatin, vasoactive intestinal peptide, and synaptophysin [395,396]. Some studies have also identified polysialic acid (neural cell adhesion molecule) in medullary carcinomas but not in other thyroid tumors [397].

Occasional lesions (and often these are small cell type) do not contain immunoreactive calcitonin. In order to accept a calcitonin-free tumor of the thyroid as a medullary carcinoma, it should arise in a familial setting or occur in a thyroid with unequivocal C cell hyperplasia [398]. Immunoreactivity for calcitonin gene-related peptide would add proof to the histogenetic nature of such a lesion.

Prognostic Factors

From the clinical standpoint, stage is the most important variable for prognosis [399–401]. A tumor confined to the thyroid without nodal or distant metastases is associated with prolonged survival. Several workers have found that younger patients (under age 40), especially women, fare somewhat better than the whole group of medullary cancer patients [399,402]. Patients who are discovered by screening because they are members of affected families often have very small tumors and can be cured by thyroidectomy. Patients with Sipple's syndrome tend to have less aggressive tumors than the sporadic group whereas the patients with MEN type 2B have aggressive lesions [401,403,404]. Pathologic features that have been related to prognosis include tumor pattern, amyloid content, pleomorphism, necrosis, mitotic activity, and DNA aneuploidy [405].

Mixed Follicular and Medullary Carcinoma

These controversial tumors show thyroglobulin and calcitonin immunoreactivity and ultrastructural evidence of differentiation along two cell lines. Some of the series of these tumors may have been confusing, with trapping of follicles at the invading edge of the medullary carcinoma and diffusion of thyroglobulin into the medullary carcinoma; this may result in diagnosis of mixed tumors showing immunostaining for both hormones. Caution should be taken when making the diagnosis of mixed medullary and follicular-derived carcinomas [406–409].

Micromedullary Carcinoma

A few medullary carcinomas are discovered incidental to thyroid operations for other conditions, at autopsy, or because of an elevated serum calcitonin. The so-called *micromedullary carcinomas* (equivalent to micropapillary carcinoma and defined as tumors of 1 cm or less) have an excellent prognosis if confined to the gland [410,411]. Some of the micromedullary cancers arise in the background of chronic thyroiditis

and may be associated with C cell hyperplasia even in the absence of familial disease [412]. Some of these patients have hypothyroidism and elevated TSH levels. Hence this type of C cell hyperplasia and micromedullary carcinoma may represent a secondary "reactive" phenomenon leading to early neoplastic change [410,412–414]. The non-tumoral parenchyma should be examined for evidence of C cell hyperplasia in a thyroid removed for a medullary carcinoma. Occasionally, the gland contains moderate to severe autoimmune thyroiditis, adenomatoid nodules, or another follicular-derived thyroid cancer [414–416].

10.7.3 Lymphoma

Secondary involvement of the thyroid by lymphoma has been reported in 20% of patients dying from generalized lymphoma. Primary lymphoma of the thyroid is uncommon but not rare. Most patients may have a history of diffuse goiter (probably the result of autoimmune thyroiditis) that has suddenly increased in size.

Most thyroid lymphomas are diffuse in type. Virtually all examples are B cell types; many may be extranodal lymphomas that arise in mucosa-associated lymphoid tissue (MALT) especially in the gastrointestinal tract. Some patients have typical plasmacytomas and these have a good prognosis. Hodgkin's disease is extremely rare. Malignant lymphoma should be differentiated from advanced autoimmune thyroiditis; this distinction requires assessment of lymphocyte clonality by special studies (e.g., flow cytometry, gene rearrangement) [106,107,417–419].

10.7.4 Thyroid Tumors in Unusual Locations

Although clinically significant *lingual thyroid* is an unusual disorder, and microscopic remnants of thyroid tissue have been described in 9.8% of tongues examined at autopsy. Rare cases of thyroid carcinoma arising in lingual thyroid are recorded [420].

Neoplasms arising in association with the *thyroglossal duct* might be expected to be squamous carcinomas, but these are extremely rare; indeed, most tumors occurring in this setting have been thyroid carcinomas and most are described as papillary. Medullary carcinoma has not been described; since the parafollicular cells are not found in the median thyroid, this is not unexpected. The clinical presentation of thyroglossal duct carcinoma is identical to that of benign thyroglossal duct cysts, i.e., a swelling in the anterior neck [27,421,422].

When the diagnosis of thyroglossal cyst-associated thyroid cancer is made, the question of its origin arises. Does this tumor represent a metastasis from a primary lesion in the gland, or is the primary site in the region of the gland, or is the primary site in the region of the cyst? In rare cases in which the thyroid was examined pathologically, areas of papillary carcinoma were found in the gland [30,423]. Most authors studying this problem conclude that the thyroglossal carcinoma is a primary tumor arising in remnants of thyroid associated with the duct; in those few cases where intrathyroidal tumor has been found, this was considered a separate primary [30,421] although molecular analyses have not yet been reported to settle this question.

Malignant tumors arising in thyroid tissue located within the trachea or larynx are very rare, but have been reported [424].

Carcinomas, usually papillary subtype, and lesions that resemble carcinoid tumors can arise in struma ovarii [425–427].

10.7.5 Metastatic Neoplasms

Tumors metastasize to the thyroid via direct extension from tumors in adjacent structures, by retrograde lymphatic spread, or hematogenously. Carcinomas of the larynx, pharynx, trachea, and esophagus can invade the thyroid directly. In these cases the distinction from a thyroid primary is usually not difficult. Retrograde extension via lymphatic routes into the thyroid is unusual. In theory, at least, any tumor involving cervical lymph nodes could extend into the thyroid by this mechanism. Hematogenous metastases to the thyroid vary according to tumor type [329]. Carcinomas of the kidney, lung, and colon and melanoma are most commonly found [329]. Such lesions are often solitary, circumscribed masses; they may appear quite compatible with a primary tumor. Resemblance to colonic adenocarcinoma, breast cancer, or pigmented melanoma reassures that this is a metastasis. However, clear cell carcinoma of the kidney, as noted above, may present a problem [329,428–430].

10.8 Frozen Section Diagnosis and the Thyroid

Before the advent of fine- and large-needle biopsy, the method most often used in diagnosis of thyroid nodules was intraoperative frozen section. The nodule or preferably the thyroid lobe was excised and a representative portion (preferably encompassing nodule

capsule–thyroid interface) was prepared for frozen section and interpretation by a pathologist. In those cases in which the diagnosis of papillary, medullary, or anaplastic cancer was given, appropriate surgery was immediately undertaken.

Even with frozen section, however, despite recommendations of sampling two or even four different areas, the diagnosis of follicular carcinomas was notoriously difficult. In many cases, the diagnosis rendered is "follicular lesion diagnosis deferred to permanent sections" [299,300,431].

Several studies have evaluated frozen section and fine-needle aspirate (FNA) diagnostic results for thyroid nodules [432–434]. Although frozen section diagnosis may be specific (90–97%), it is not sensitive (60%). In addition, deferred diagnoses at frozen section do nothing to alter the operative procedure or guide the surgeon [299]. Frozen section results influenced the surgical approach in only a small percentage of cases. Also, in the era of cost containment, it does not seem justified to perform frozen sections for the intraoperative diagnosis of thyroid nodules; the initial approach to a thyroid nodule should be an aspiration biopsy (FNA) [299,435,436]. If the diagnosis rendered on FNA is definitely malignant, the surgeon should proceed with the appropriate surgery for that malignant diagnosis. If the FNA diagnosis is suspicious for malignancy, and that the suspected lesion is papillary carcinoma or a variant thereof, intraoperative frozen section may be useful since the diagnosis relies on the nuclear morphology and not the finding of invasion. If the FNA diagnosis is "neoplasm" and therefore non-committal as to the type, frozen section will not provide a definitive diagnosis and therefore should not be requested [37,248,251,437].

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