23 Thyroid

The thyroid has two basic cell types: the follicular epithelium (TTF-1 and thyroglobulin positive) and the C cells (TTF-1, neuroendocrine-marker, and calcitonin positive; thyroglobulin negative). Normal follicular epithelium is low cuboidal. The stroma or interstitium is scant but highly vascular.

Inflammatory diseases of the thyroid are rarely seen in surgical pathology, with a few exceptions detailed in this chapter. Conceptually, they can be classified by type of response:

- Acute inflammation and necrosis: acute thyroiditis
- Foreign body giant cells and lymphocytes, diffuse: subacute thyroiditis (de Quervain's syndrome)
- Histiocytes, lymphocytes, and rare giant cells, focal: palpation thyroiditis (a reaction to physical trauma, not a primary inflammatory disease)
- Lymphocytic infiltrate with germinal centers: lymphocytic thyroiditis or Hashimoto's thyroiditis
- Dense fibrosis and chronic inflammation: sclerosing Hashimoto's versus fibrosing thyroiditis (Riedel's, a very rare entity)

Lymphocytic thyroiditis is a descriptive term implying a generalized lymphocytic infiltrate. The term *Hashimoto's thyroiditis* refers to an autoimmune process attacking the thyroid, and it is characterized by the following:

- Prominent lymphoplasmacytic infiltrate with germinal center formation (Figure 23.1)
- Small, atrophic follicles with Hurthle cell change (oncocytic change)

Scattered nuclear atypia may be seen in this setting, including large hyperchromatic Hurthle cell nuclei, as well as areas of nuclear clearing and pleomorphism that can simulate papillary carcinoma. Therefore, be cautious about diagnosing papillary carcinoma in the setting of lymphocytic thyroiditis. *However*, these patients can also get papillary carcinoma!

Graves' disease (diffuse toxic hyperplasia) is a hyperplastic, hyperthyroid condition in which autoantibodies stimulate the thyroid-stimulating hormone receptor to produce excess thyroid hormone. In treated form, more commonly seen in pathology, the follicles are large and distended, with prominent papillary infoldings (Figure 23.2). The papillary architecture can become florid, but the nuclear features are not those of papillary carcinoma (discussed later). Scalloping of the colloid is prominent. In untreated Graves' disease, on the other hand, the thyroid is highly cellular with minimal colloid.

Goiter is a nonspecific term for enlargement (hyperplasia) of the thyroid but is often used to refer to the nodular enlargement of the thyroid due to iodine deficiency (endemic goiter) or enzyme defects (sporadic goiter). *Multinodular hyperplasia* may be sampled by fine-needle aspiration (FNA) if a single nodule becomes dominant and suspicious, or the whole gland may be removed for cosmetic or physiologic reasons. The nodules usually fall on the colloid nodule-to-follicular adenoma spectrum (see later).

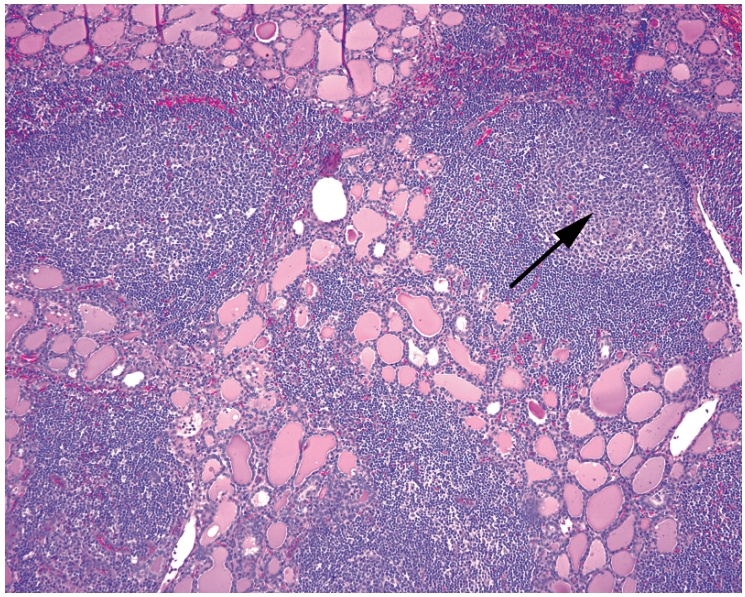

FIGURE 23.1. Hashimoto's thyroiditis. The thyroid follicles are displaced by germinal centers (arrow).

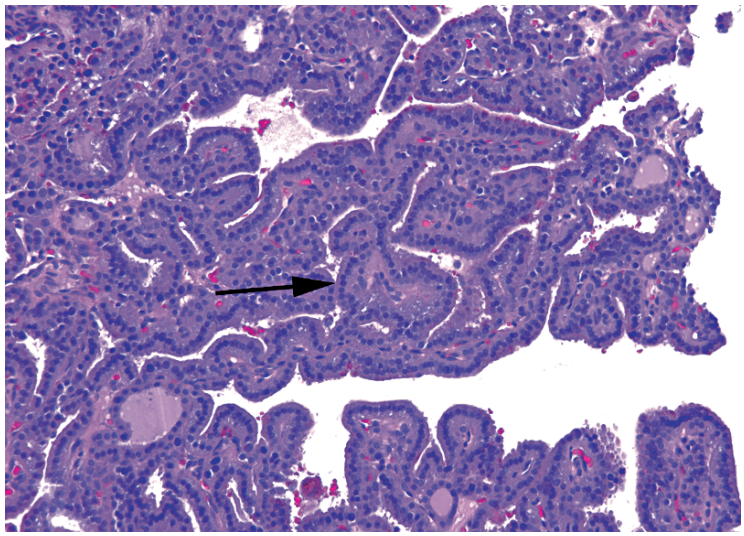

FIGURE 23.2. Graves' disease with papillary hyperplasia. These papillary formations are due to hyperplasia of the follicular epithelium. The follicular cells are round, fairly evenly spaced, and have dark uniform chromatin (arrow), similar to normal follicles.

The world of thyroid neoplasms can be broken down into several large categories. The first two categories arise from follicular epithelium, and they are divided in this chapter into two groups based on cytologic and nuclear features. The first category is made up of follicular-type cells that resemble normal thyroid follicular epithelium. This category includes Hurthle cells, which can be found in nonneoplastic thyroid. The second major category is the papillary carcinoma group, of which there are many variants; they have in common a set of diagnostic nuclear features. The third category of neoplasms arises from the *neuroendocrine* or C cell component of the thyroid; medullary carcinoma is the main entity in this group. Table 23.1 summarizes the architectural and cytologic features of thyroid neoplasms.

Follicular-Type Lesions

Follicular-type cells are notable for their uniformity. The nuclei tend to be round and monotonous, although they may be enlarged compared with normal thyroid. The overall impression is that of a regular array of cells, without crowded, overlapping, or irregular nuclei (Figure 23.3). The cells should respect each others' personal space, so to speak. The chromatin should be even and smooth, not cleared out, coarse, or chunky.

Colloid nodule, adenomatoid nodule, and *follicular adenoma* all describe a spectrum of hyperplastic to neoplastic lesions composed of a nodular cluster of follicular epithelium. This area is somewhat confusing as the same lesion may get different names depending on whether it is seen by FNA or on resection. A *colloid nodule* is a hyperplastic nodule of large distended follicles in which the ratio of colloid to cells is high (a key finding on FNA). A *follicular adenoma* is defined as a solitary encapsulated nodule with compression of the surrounding thyroid and is usually composed of small microfollicles with scant colloid (a low colloid to cell ratio; Figure 23.4). This lesion, seen on FNA, is called a *follicular neoplasm*, as follicular

Table 23.1. Summary of architectural and cytologic features of thyroid neoplasms.

	Macro- or normofollicular nodule	Microfollicular nodule	Papillary pattern	Solid or nested growth
"Follicular" nuclei	Hyperplastic nodule or Follicular adenoma	Follicular adenoma/ carcinoma	Graves' disease	Insular carcinoma
Hurthle cells	Hurthle cell adenoma	Hurthle cell adenoma/ carcinoma	Oncocytic variant of papillary carcinoma	
"Papillary" nuclei	Follicular variant of papillary carcinoma	Follicular variant of papillary carcinoma	Papillary carcinoma	
Pleomorphic cells				Anaplastic carcinoma
Neuroendocrine nuclei				Medullary carcinoma

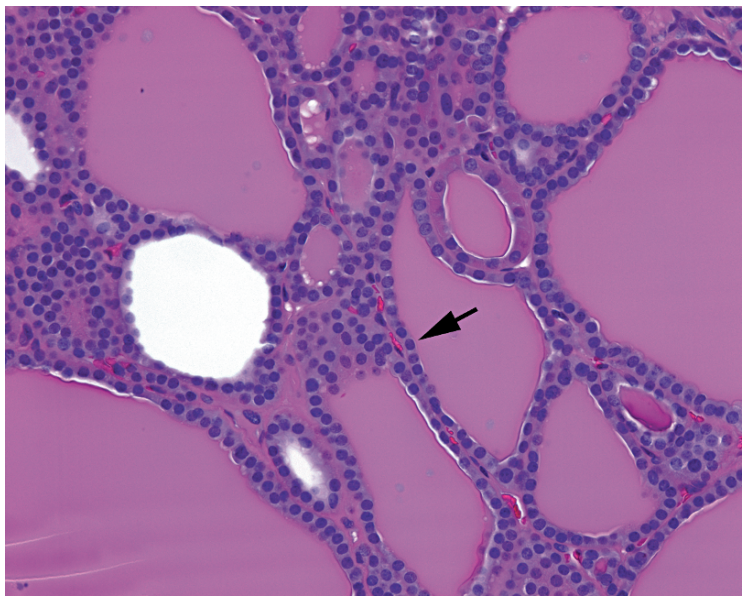

Figure 23.3. Follicular cells. Normal follicular epithelium has round uniform nuclei that tend not to overlap or crowd each other (arrow). This field is a combination of large and small follicles full of colloid and could represent normal thyroid, nodular hyperplasia, or a follicular neoplasm.

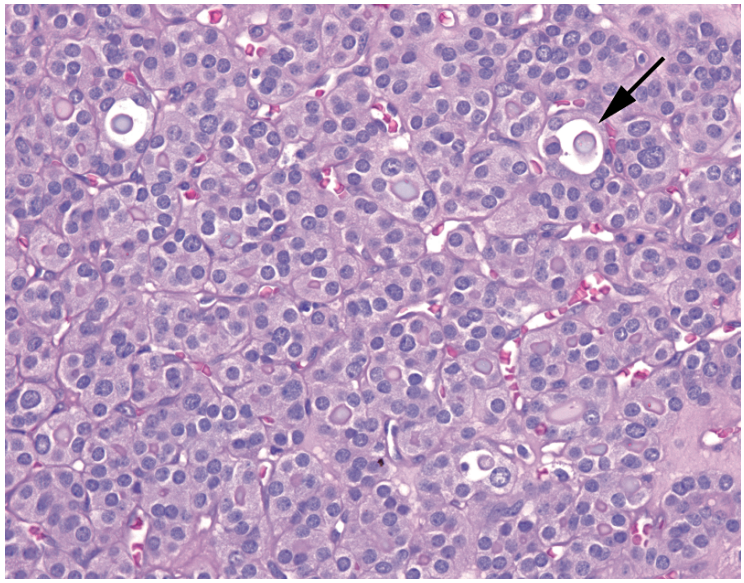

FIGURE 23.4. Follicular adenoma. This field shows a microfollicular pattern in a follicular adenoma. The capsule is not seen here. The neoplasm is composed of tightly packed small follicles (arrow) with round nuclei that, like normal follicular epithelium (see Figure 23.3), tend not to overlap or crowd. There are scattered enlarged nuclei, some with pale chromatin that should not be mistaken for true nuclear clearing.

adenoma and carcinoma can not be distinguished by FNA alone. Finally, there is the *adenomatoid nodule*, a hyperplastic lesion that has some features of the adenoma.

Before calling a lesion a follicular adenoma, however, you must submit and examine the entire capsule. Follicular carcinoma may appear histologically similar to adenoma but for the diagnostic capsular or vascular invasion. This is why you cannot make the distinction by FNA alone. You should also exclude the follicular variant of papillary carcinoma (discussed later).

Hurthle cell adenoma is very similar to a follicular adenoma in concept except the cells are large pink oncocytes with round nuclei (Hurthle cell change; Figure 23.5). Nucleoli may be prominent, and the nuclei may appear very enlarged or irregular in shape, unlike in follicular adenoma. As with follicular neoplasms, evaluating the capsule is key to calling it benign or malignant.

The defining feature of a *follicular carcinoma* (or Hurthle cell carcinoma) is the presence of capsular or vascular invasion, so examination of the capsule is critical. Atypia and necrosis, while seen in follicular carcinoma, are not sufficient to make the diagnosis.* Capsular invasion is a controversial area, and experts disagree on the exact criteria that define it; however, a mushrooming growth of tumor through the capsule is accepted by most. Vascular invasion must be found within the capsule itself or outside the capsule. The tumor deposit should be visibly attached to the vessel wall (Figure 23.6).

Follicular carcinoma comes in two strengths: minimally invasive (where you have to struggle to find the diagnostic vascular invasion) and widely invasive (where you have to dissect it off the adherent neck structures). It is not associated with radiation or thyroiditis, unlike papillary carcinoma. It spreads via the blood to lung and bone.

Insular carcinoma is rarely diagnosed and can be thought of as a poorly differentiated carcinoma. The cells grow in sheets and cords (insular pattern; Figure 23.7) and on high power resemble the round and uniform cells of follicular carcinoma. Pleomorphism is not a typical feature here, but mitoses, necrosis, vascular invasion, and infiltrative growth *are* common.

**Random pearl*: In this, the thyroid is like most other neuroendocrine organs, including parathyroid, adrenal, and pituitary. The diagnosis of malignancy is not based on atypia, which can be seen in hyperplastic conditions, but on capsular/vascular invasion or metastases.

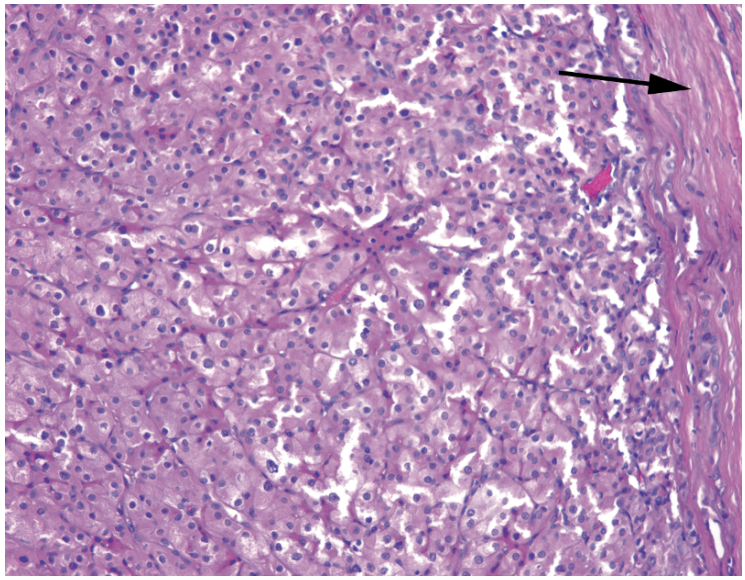

Figure 23.5. Hurthle cell adenoma. Like follicular adenomas, there is a thick fibrous capsule surrounding the neoplasm (arrow). In a Hurthle cell adenoma, the cells have abundant pink cytoplasm, and, although the nuclei are still overall round and nonoverlapping, there is increased nuclear atypia in the form of some prominent nucleoli and irregular nuclear shapes.

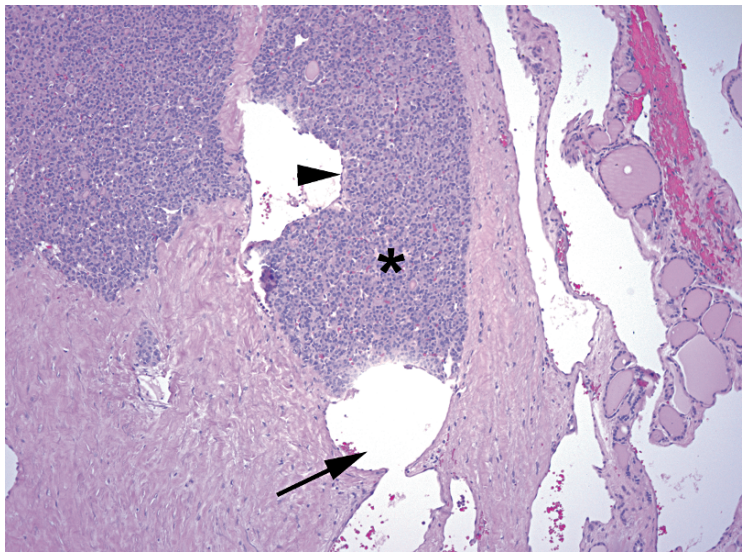

Figure 23.6. Follicular carcinoma. The neoplasm here resembles a follicular adenoma at low power, with a dense microfollicular pattern and a thick capsule. However, there is vascular invasion in the capsule, diagnostic of follicular carcinoma. A tumor plug (asterisk) is seen in the lumen of a large vessel (arrow). The surface of the tumor plug becomes endothelialized (arrowhead).

Papillary Carcinoma

Papillary carcinoma (there is no papillary adenoma), despite the name, may come with or without the papillae. The diagnosis actually rests on the nuclear features, which are consistent across variant types. The nuclear features are as follows:

- Chromatin is cleared out (resembling orphan Annie eyes). This imparts a characteristic low-power look to the lesion; the cells stand out as crisp and pale, almost glittery or glassy (Figure 23.8). It is an artifact of formalin.

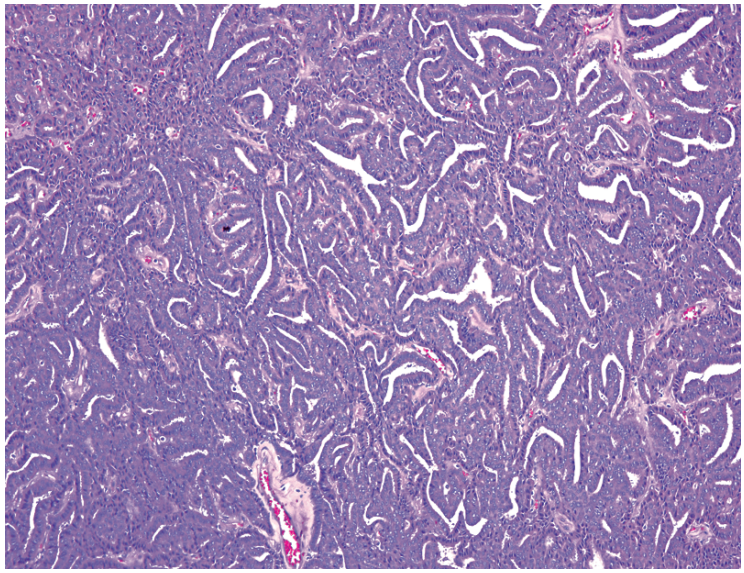

Figure 23.7. Insular carcinoma. Instead of microfollicles, the tumor has acquired a pattern of ribbons, cords, and slit-like spaces.

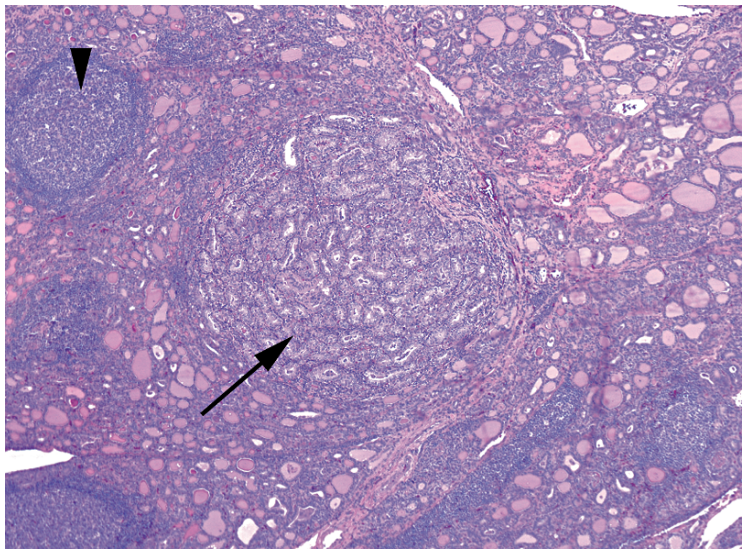

Figure 23.8. Papillary carcinoma, low power. The nuclear features of papillary carcinoma are eye-catching even at low power, as the clear nuclei give a translucent or glassy appearance to the tumor nodule (arrow). This is an example of an incidental microcarcinoma, arising in Hashimoto's thyroiditis (note germinal centers, arrowhead).

- Nuclei are overlapping, crowded, and pleomorphic. They often appear boxy and angular at low power, and you get the impression that too many nuclei have been stuffed into a single row (Figure 23.9); some are squeezed up and out of the row.
- Nuclear grooves (having a coffee bean appearance) are present.
- Nuclear pseudoinclusions (basically indentations of cytoplasm) are present.

Note that prominent nucleoli are not a feature of papillary carcinoma. Psammoma bodies are fairly specific for papillary carcinoma but are generally seen only in the context of papillary architecture. True psammoma bodies are dark purple, ringed like a tree, and usually found in the interstitium, not in follicles (Figure 23.10). There are several variants of papillary carcinoma.

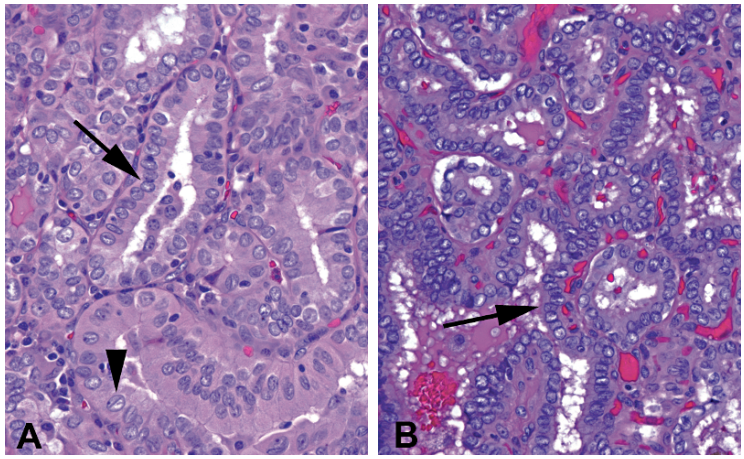

Figure 23.9. Papillary nuclei. **(A)** In this example, although the nuclear clearing is not striking, the presence of oval nuclei crowded into a row (arrow) suggests papillary carcinoma, as does the presence of nuclear grooves (arrowhead). Compare these nuclei to those of follicular epithelium see (Figure 23.3). **(B)** In this lesion the nuclear clearing is much more evident. However, the nuclei are still oval in shape and crammed together such that they mold to each other, popping up and out of their crowded rows (arrow).

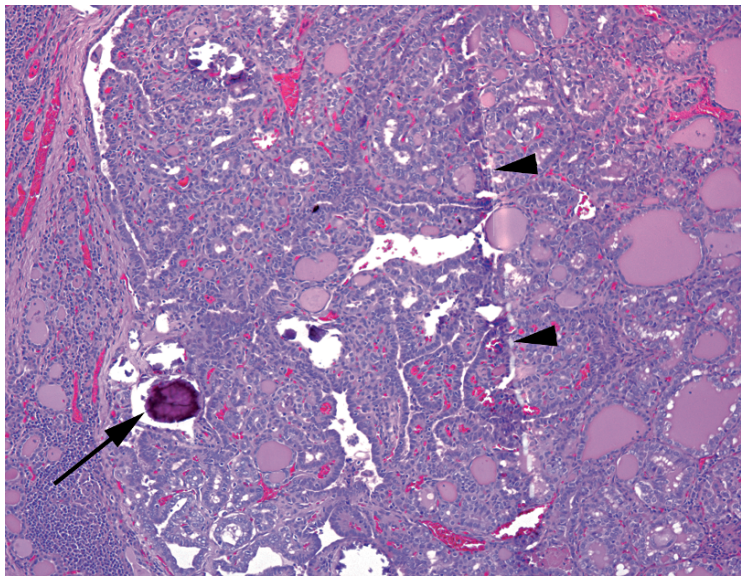

Figure 23.10. Psammoma body. This dense purple laminated calcification (arrow) is virtually diagnostic of papillary thyroid carcinoma in the thyroid or in a neck lymph node. Telltale scratches in the tissue section (arrowheads) often show where a psammoma body was dragged across the block during sectioning.

- Papillary microcarcinoma: Although histologically identical to papillary carcinoma, papillary microcarcinomas are less than 1 cm (by definition), usually incidentally discovered, and, if solitary, are considered clinically benign.
- Follicular: The follicular variant is a lesion with follicular architecture (no papillae) and papillary nuclei (Figure 23.11). It behaves like a papillary carcinoma and is now signed out as one. Differentiating between a follicular adenoma and a follicular variant of papillary carcinoma is no trivial task, as the nuclear changes can be patchy. Beware fixation artifact (which can produce nuclear clearing but not the other features) and lymphocytic thyroiditis (which produces reactive changes that can simulate papillary nuclei).

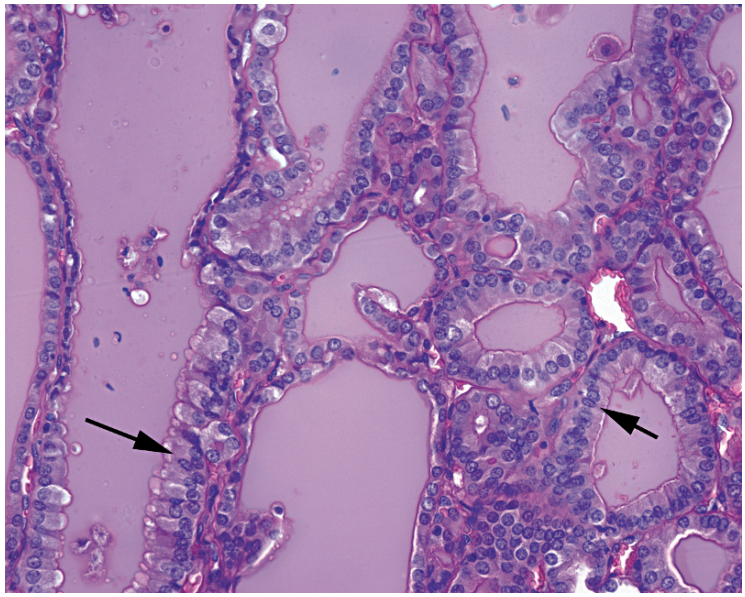

Figure 23.11. Follicular variant of papillary carcinoma. The architecture is that of a follicular adenoma, but the nuclei, oval in shape and crowded together (arrows), are those of papillary carcinoma.

- Diffuse sclerosing variant: Although rare, the diffuse sclerosing variant is important to recognize because of its worse prognosis. You can think of this variant as being widely infiltrative in its behavior, as opposed to discrete and mass-forming, and therefore more aggressive. The features include a desmoplastic or sclerotic stroma, squamous metaplasia, psammoma bodies, a dense lymphocytic infiltrate, and vascular invasion.
- Others: Other variants include tall cell, columnar cell, trabecular, cribriform, and cystic variants.

Anaplastic carcinoma is often a papillary carcinoma that has dedifferentiated (Figure 23.12). The tumor cells may appear as sheets of pleomorphic cells (truly undifferentiated), as nonkeratinizing squamous cell carcinoma (squamoid differentiation), or sarcomatoid. A background of papillary carcinoma is not uncommon, but anaplastic carcinoma may arise from other types of carcinoma as well.

The most important lessons of the papillary variants are these: not all papillary lesions are papillary carcinoma (Graves' disease, for example), and not all papillary carcinomas have papillary architecture (follicular variant, for example). Also, not all cleared out nuclei are papillary carcinoma. Beware fixation artifact (as discussed earlier), and have a very high threshold of suspicion for papillary carcinoma in the setting of lymphocytic (Hashimoto's) thyroiditis. A true carcinoma arising in Hashimoto's thyroiditis should stand out sharply from its neighbors, as in an uninflamed thyroid (see Figure 23.8). Varying degrees of nuclear clearing that come and go across the section are likely to be insignificant.

Papillary carcinomas are associated with radiation and (possibly) thyroiditis as risk factors; unlike follicular carcinoma, they spread to lymph nodes. The prognosis is usually excellent. Age is the most important prognostic factor (younger is better).

Neuroendocrine Lesions

Medullary carcinoma has features common to other neuroendocrine tumors; the growth may be nested or trabecular, and the cells range from epithelioid to spindled, with uniform finely speckled nuclei (Figure 23.13). At low power, or with poor histology, the sheet-like growth may simulate an anaplastic carcinoma. However, nuclear features or immunohistochemistry should easily tell the difference (calcitonin positivity and thyroglobulin negativity should do it). Medullary carcinomas produce prominent amyloid, which is Congo-red positive.

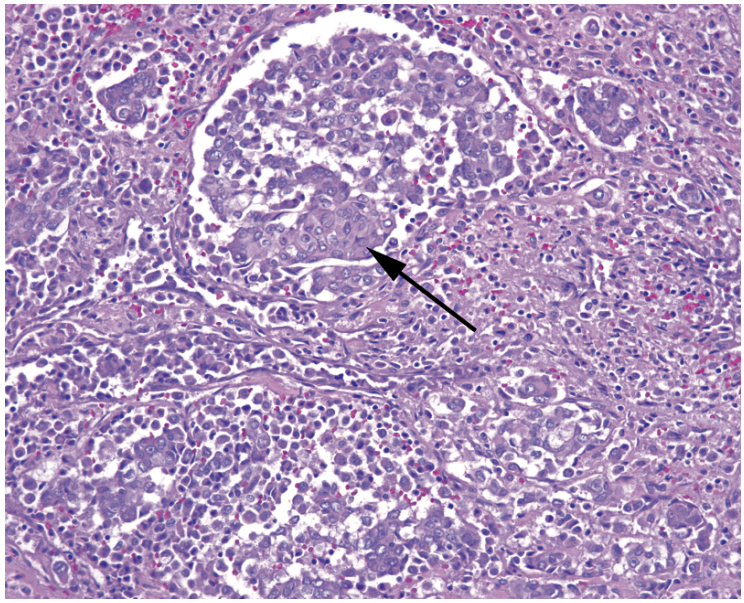

Figure 23.12. Anaplastic carcinoma. Nests and sheets of poorly differentiated carcinoma, some areas with a squamoid appearance (arrow).

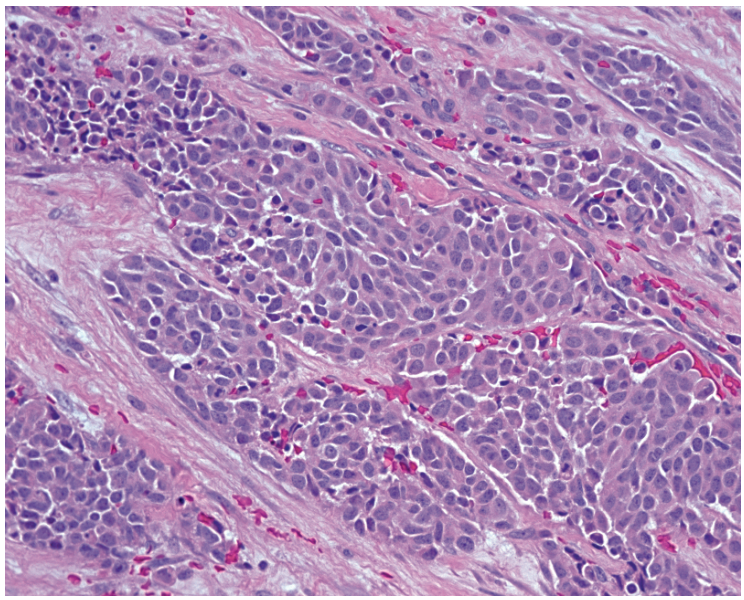

Figure 23.13. Medullary carcinoma. Although the pattern of infiltrative nests of cells may resemble anaplastic carcinoma, the nuclei are much more bland, with pale, finely speckled, neuroendocrine-type chromatin.

Cystic Nonneoplastic Lesions of the Neck

While not thyroid lesions, cystic nonneoplastic lesions of the neck are included here as they are commonly seen in surgical pathology and are sometimes mistaken clinically for a thyroid nodule. Such lesions include the following:

Thyroglossal duct cyst: a midline structure (as are the thyroid and the tongue) consisting of a cyst lined by ciliated epithelium and thyroid follicles

Branchial cleft cyst: an anterolateral structure (as are the branchial clefts) that looks somewhat tonsillar: squamous, columnar, or ciliated epithelium with a dense underlying lymphocytic infiltrate (*not* bronchial [i.e., lung] or brachial [i.e., arm])