The Thyroid Hürthle (Oncocytic) Cell and Its Associated Pathologic Conditions

A Surgical Pathology and Cytopathology Review

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Context.—Hürthle cells are eosinophilic, follicular-derived cells that are associated with a variety of nonneoplastic and neoplastic thyroid lesions. The differential diagnosis of Hürthle cell lesions is quite broad.

Objective.—To review the pathologic conditions associated with Hürthle cells in the thyroid and to discuss pathology of thyroid lesions associated with oncocytic cytology.

Data Sources.—A variety of thyroid nonneoplastic (autoimmune thyroiditis, multinodular goiter) and neoplastic conditions (Hürthle cell adenoma, Hürthle cell carcinoma) are associated with Hürthle cell cytology. In addition, there are several thyroid neoplasms that should be considered when one observes a Hürthle cell neoplasm in the thyroid (oncocytic variant of medullary carcinoma, several variants of papillary thyroid carcinoma).

Conclusions.—Oncocytic cytology is seen in a variety of thyroid conditions that are associated with a broad differential diagnosis and care must be used for accurate diagnosis. Newer molecular-based techniques may be useful for further classification of thyroid neoplasms with oncocytic pathology.

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zymes of the mitochondrial respiratory chain have also been reported in Hürthle cell neoplasms.\textsuperscript{13,14} It has been postulated that due to a decrease in mitochondrial activity secondary to DNA alteration, mitochondria proliferate resulting in an overall increase in their number.\textsuperscript{14} The process of mitochondria accumulation in the cytosol of follicular epithelial cells does not occur rapidly. It is believed to occur slowly over time, which explains why Hürthle cells are rarely seen in nonneoplastic and neoplastic lesions in children.\textsuperscript{13} In addition, accumulations would be most evident in cells with a low turnover rate such as follicular epithelial cells. Rapidly dividing cells would prevent the accumulation of mitochondria.

**NONNEOPLASTIC ENTITIES ASSOCIATED WITH HÜRTHLE CELL METAPLASIA**

Hürthle cells are present in a variety of nonneoplastic conditions involving the thyroid and are not specific for any disease process. Hürthle cell metaplasia is seen in a variety of benign conditions such as autoimmune thyroiditis and multinodular goiter and in thyroids of patients that have been treated with head and neck irradiation and systemic chemotherapy.\textsuperscript{15-21} (Figure 2, A). In addition, the thyroids of patients with long-standing hyperthyroidism (Graves disease) may show focal or diffuse Hürthle cell change\textsuperscript{20} (Figure 2, B). In fact, Askanazy originally described these cells in thyrotoxicosis.\textsuperscript{2} Hürthle cells also increase with aging.\textsuperscript{20} In some instances, one can often find an entire nodule composed of oncocytes and the distinction of hyperplasia from neoplasia can be problematic.

In many of these nonneoplastic conditions, Hürthle cells are found as isolated cells or lining one to a few follicles, but in some cases, an entire nodule may be composed of oncocytes. The classic thyroid disorder in which Hürthle cells are prominent is chronic lymphocytic thyroiditis with oxyphilia (Hashimoto disease). In virtually all cases of classic and fibrosing variants of chronic lymphocytic thyroiditis, most or all of the follicular epithelium takes on Hürthle cell cytology.\textsuperscript{20} In fact, in our opinion, the diagnosis of classic Hashimoto thyroiditis should show the triad of lymphocytes, plasma cells, and Hürthle cells.

Most of the conditions associated with Hürthle cell.
change are chronic, suggesting the possibility that alteration in the follicular epithelium to take on Hürthle cell histology requires chronic stimulation.\textsuperscript{15,18}

\textbf{ONCOCYTIC THYROID NEOPLASMS}

\textbf{Hürthle Cell Neoplasms: General Concepts}

Although oncocytic thyroid neoplasms encompass a variety of phenotypes according to the current World Health Organization classification,\textsuperscript{22} the lesions that have produced the most debate are those with a follicular and solid pattern and the ones to which most pathologists refer to as Hürthle cell neoplasms.

As noted previously, not all nodules of Hürthle cells are neoplastic. In fact, adenomatous Hürthle cell nodules are common in multinodular goiter and are quite frequently seen in autoimmune thyroiditis. There has been considerable debate about whether these represent true neoplasms. We feel these nodules are metaplastic and should not be included in studies discussing Hürthle cell neoplasms. Hürthle cell nodules are distinguished from Hürthle cell neoplasms by the absence of a complete lesion capsule. Some experienced pathologists believe that Hürthle cell nodules in thyroiditis can be distinguished as metaplastic or neoplastic by the presence of intraleisional lymphocytes in the former. Although there is a trend in this direction, our experience is that this is not an absolute criterion as we have recognized angioinvasive Hürthle cell carcinomas arising in chronic thyroiditis in which lymphocytes were percolating through the cords of tumor cells.

By definition, Hürthle cell neoplasms are composed of 75\% or greater Hürthle cells. A variety of thyroid neoplasms are characterized as having oncocytic cytology. These include benign (Hürthle cell adenoma, granular cell tumor) and malignant (Hürthle cell carcinoma) neoplasms, variants of papillary thyroid carcinoma (PTC) (tall cell variant, oncocytic variant, and Warthin-like variant), and the oncocytic variant of medullary carcinoma.

There was a significant debate in the early endocrine and surgery literature on the incidence of malignancy in Hürthle cell neoplasms.\textsuperscript{23-48} Some authors cite that 80\% or more of these lesions are benign (especially when studies have included Hürthle cell adenomatous nodules), whereas others considered all Hürthle cell neoplasms as malignant. The latter finding was proposed because the initial studies on Hürthle cell tumors showed that even lesions that were initially diagnosed as benign acted in a malignant fashion. Throughout the years though, with good follow-up studies and refinement of the criteria for malignancy in encapsulated thyroid neoplasms such as capsular and/or vascular invasion as well as the establishment of molecular techniques that have identified oncogenic follicular variants of papillary carcinoma, it has been clearly established that there are Hürthle cell neoplasms that act in a benign fashion as well as those that act in a malignant fashion.\textsuperscript{34,36,44-48}

Studies that include multiple Hürthle cell nodules found in the background of goiter or chronic lymphocytic thyroiditis indicate that more than 80\% of Hürthle cell neoplasms are benign.\textsuperscript{28,32,40} However, other studies that exclude these unencapsulated Hürthle cell nodules have shown that the rate of malignancy is higher in Hürthle cell than classic follicular neoplasms (2\%-3\% vs 30\%-45\%).\textsuperscript{34,36,44-48}

Grossly, Hürthle cell neoplasms are usually solitary and show at least partial encapsulation. They are distinctly mahogany brown due the abundant mitochondrial cytochrome content. Lesions may vary significantly in size from one to several centimeters. Similar to oncocytic neoplasms in other organs, a central scar may be evident. Hemorrhage and necrosis may be grossly seen especially in lesions that have undergone preoperative fine-needle aspiration biopsy; massive infarction either spontaneously or following fine-needle aspiration biopsy has been reported in Hürthle cell tumors.\textsuperscript{49-51} The infarction can be extensive, leading to severe hampering of the histologic assessment. The presence of spontaneous infarction does not equate with malignancy.

Microscopically, Hürthle cell neoplasms should be composed of at least 75\% Hürthle cells. A variety of patterns of growth may be seen such as macrofollicular, follicular, trabecular, solid, and pseudopapillary.\textsuperscript{24} Many tumors will show a variety of these patterns of growth. The pattern of growth is usually follicular, but it also can be trabecular or solid. Hürthle cell neoplasms, both benign and malignant, have a tendency to show pseudopapillary change, which is felt to be an artifact from fixation and tissue processing. Hürthle cell neoplasms may show dystrophic calcifications, which may even be psammomatous in nature. Importantly, these psammoma-like or pseudopsammoma bodies are present within colloid and are often not lamellated.\textsuperscript{20,21} (Figure 3). We consider these calcifications to represent an unusual reaction in the micro milieu in which biochemically modified colloid produced by the Hürthle cells attracts calcium, which precipitates in it. Psammoma bodies in epithelial cells or in the thyroid interstitium should alert the pathologist to the high probability of papillary carcinoma elsewhere in the gland.

One of the most difficult aspects of examining Hürthle cell neoplasms is to determine whether the lesion is benign or malignant. Size in and of itself is not predictive of behavior, although larger lesions have a higher incidence of malignancy.\textsuperscript{34,36,44-48} It is quite clear that pathologic criteria for malignancy, such as vascular and capsular invasion, can predict the clinical behavior of these tumors.\textsuperscript{34,36,44-48} Nuclear atypia, multinucleation, cellular pleomorphism, mitoses, or histologic pattern of the lesion are not determinants of malignancy.\textsuperscript{44} The main criteria for malignancy include the presence of capsular and/or vascular invasion (Figure 4, A through C). Like follicular carcinomas, Hürthle cell carcinomas can be classified as minimally invasive, angioinvasive (invasion of vessels in and/or beyond the lesional capsule), or widely invasive. Minimally invasive tumors show invasion into and/or though the lesional capsule focally. In our opinion, minimally invasive tumors should not have evidence of angioinvasion. Using this strict definition, the prognosis of minimally invasive Hürthle cells should be excellent. Tumors with minimal capsular invasion but evidence of vascular invasion should be classified as angioinvasive and the number of foci of vascular invasion quantified if possible. Ghossein et al\textsuperscript{52} recently reported on 50 patients with encapsulated Hürthle cell carcinomas. They identified the most important risk factor for recurrent disease was the presence of vascular invasion. More specifically, 4 or more areas of vascular invasion was associated with a significantly higher risk of recurrence in otherwise encapsulated Hürthle cell carcinomas. Widely invasive tumors have extensive encapsulation and vascular invasion.
As noted previously, Hurthle cell neoplasms have a tendency to undergo spontaneous necrosis or show extensive degenerative necrosis following fine-needle aspiration biopsy. In these situations, viable lesional cells are often not present and it is difficult to fully evaluate the lesion pathologically. Therefore, it may be very difficult for the pathologist to determine whether the lesion is benign or malignant. In our opinion, unless there is unequivocal vascular invasion seen in the tumor capsule or beyond, the pathologist should not diagnose carcinoma in an otherwise infarcted Hurthle cell tumor. Our recommendation for reporting in these situations is as follows: “completely necrotic thyroid neoplasm without evidence of definitive vascular invasion” with a comment explaining that it is difficult to determine the behavior of this completely infarcted tumor.

It is believed by some authors that transformation of poorly differentiated and anaplastic forms may occur in some Hurthle cell carcinomas. This is supported by the rare finding of Hurthle cell tumors in association with anaplastic carcinomas (Figure 5). This association has led to the speculation that Hurthle cell neoplasms can behave in a manner similar to low-grade papillary and follicular cancers, that is, they can undergo transformation to high-grade malignancies. The frequency of this occurrence is unknown and the transformation is more commonly seen in recurrences and metastases than in primary tumors.

The term atypical Hurthle cell adenoma or indeterminate Hurthle cell tumor is used to describe lesions with atypical features that do not fulfill criteria for malignancy. These features include marked cytologic atypia, mitotic activity, spontaneous infarction, necrosis, hemorrhage, and/or trapping of tumor cells within the lesion's capsule in tumors that have not been aspirated preoperatively. Long-term follow-up (median, 10–13 years) indicates that even these atypical Hurthle cell tumors behave in a benign fashion.

Although Hurthle cell carcinomas are believed to be similar to follicular carcinomas, they have a tendency to behave clinically different in some series. Metastases to regional lymph nodes are reported in Hurthle cell carcinomas (although some of these series may include oncocytic follicular variants of PTCs). In addition to lymph node metastases, Hurthle cell carcinomas spread hematogenously, most commonly to the lungs, liver, and bone. Survival rates for histologically proven carcinomas...
range from approximately 50% to 60% at 5 years; however, late recurrences and metastases are not rare.41

Flow cytometric analysis of Hürthle cell tumors indicates that this technique cannot discriminate between benign and malignant Hürthle cell neoplasms because adenomas may show aneuploidy and cancers may be diploid.26,57–60 However, in the histologically defined carcinomas, flow cytometric data may provide diagnostic aid—carcinomas that show an aneuploid pattern histologically may behave more aggressively than those that are diploid.57,58

Most patients undergo total thyroidectomy for treatment of Hürthle cell carcinoma. Following surgery, patients are often treated with iodine 131 therapy but Hürthle cells show low uptake of iodine. It is believed that stage for stage, Hürthle cell carcinomas behave more aggressively than follicular carcinomas. Nishida et al61 used a 3-tiered system and classified Hürthle cell carcinomas as “moderate” grade to recognize the clinical difference with “low grade” papillary and follicular cancers and “high grade” anaplastic tumors.

Molecular Pathology of Oncocytic Thyroid Neoplasms in General

All forms of thyroid neoplasia most likely have an oncotic component. This has been shown by several different studies. For instance, BRAF V600E mutations are seen in many usual-type PTCs as well as oncotic variants of PTC, whereas oncotic follicular variants of papillary carcinoma do not show this abnormality.52,63 In addition, ret proto-oncogene/papillary thyroid carcinoma (RET/PTC) rearrangements have been demonstrated in oncotic papillary carcinomas but not always in oncotic follicular variants of PTC.64,65 However, Cheung et al66 and Belchetz et al67 were able to reclassify follicular lesions that would have been interpreted as Hürthle cell adenomas as oncotic follicular variants of papillary carcinoma based on nuclear features and the presence of RET/PTC rearrangements. Belchetz et al67 also observed that some of their lesions with the RET/PTC rearrangements showed lymph node metastases and behaved more like papillary carcinomas. None of the Hürthle cell carcinomas or the adenomas included in their study contained RET/PTC rearrangements. Recently, Shue et al68 observed that carriers of the C allele of the common C825T polymorphism in guanine nucleotide binding protein 3 gene appear to have an increased risk of developing oncotic thyroid tumors. They propose that this polymorphism may be a factor favoring the development of oncotic thyroid tumors, although the biologic mechanism remains obscure. They believe that there may be a genetic predisposition of patients to develop oncotic thyroid neoplasms. Whether this is somehow related to the mitochondrial DNA alterations seen in oncotic thyroid tumors remains to be seen. Gasparre et al69 have recently shown that disruptive mutations in mitochondrial DNA were found in complex I subunit genes in Hürthle cell neoplasms and this finding appears to be a marker for thyroid oncotic tumors. Maximo et al70 have recently identified somatic missense mutations in GRIM19 in approximately 11% of sporadic Hürthle cell carcinomas. GRIM19 is believed to promote apoptosis as part of the interferon β and retinoic acid induced pathway of cell death, is a negative regulator of cell growth, is involved in mitochondrial metabolism, and is linked in part to mitochondrial complex I assembly. Interestingly GRIM19 is located at 19p13.2. The TCO gene locus, which has been linked to familial Hürthle cell neoplasms, has also been mapped to this locus.71,72 Baris et al73 have shown that oncotic follicular neoplasms show distinct differences in gene expression as compared with usual-type PTC. For one thing, Hürthle cell carcinomas more commonly express genes associated with mitochondrial and cellular metabolism. In addition, this group observed that overexpression of the respiratory chain complexes III and IV seems to be specific to the development of oncotic follicular carcinomas. Bonora et al74 recently have found that there are variations in the inner mitochondrial membrane transporter TIMM44 in patients with oncotic thyroid tumors. All of these studies seem to indicate that there is a genetic predisposition to develop oncotic thyroid tumors.

Oncotomatic Variant of PTC

The Hürthle cell variant of papillary carcinoma comprises approximately 10% of cases of PTC. This tumor is characterized histologically by the presence of oncotic cells with the classic nuclear features of PTC usually arising in a background of chronic lymphocytic thyroiditis with oxyphilia (Hashimoto thyroiditis).75–80 Most lesions are well circumscribed, are encapsulated, and often show at least a focal papillary growth pattern. There may be areas of follicular growth and in some cases the follicular pattern may be the predominant growth pattern. Cytologically, the tumor cells show abundant eosinophilic cytoplasm and classic papillary carcinoma nuclei as noted previously (Figure 6). In some cases, the nuclei have a tendency to localize to the apex of the cells. The differential diagnosis includes Hürthle cell neoplasms and the tall cell variant of PTC. Hürthle cell neoplasms, both benign and malignant, have a tendency to show pseudopapillary change, which is felt to be an artifact of fixation and tissue processing. The Hürthle cell variant of PTC shows true papillae with fibrovascular cores. In addition, the Hürthle cell variant of papillary carcinoma shows classic nuclear changes of PTC. The eosinophilic cells in Hürthle cell variant are not twice as tall as they are wide, a feature that aids in distinguishing this histologic variant of papillary carcinoma from the tall cell variant, which usually behaves in a much more aggressive fashion. Although the lesions are often confined to the thyroid, extrathyroidal spread as well as the presence of lymph node metastases have been reported. By molecular analysis, the oncotic variant of PTC shows RET/PTC gene rearrangements.62,63 Tovisco et al82 were able to identify BRAF mutations in oncotic variants with papillary or papillary/follicular growth, whereas tumors with just follicular growth did not show BRAF mutations suggesting that the follicular oncotic variants are genetically different from the papillary oncotic variants. Abrosimov et al81 observed MUC1 and cyclin D1 expression (a target of the Wnt pathway) in 100% of tall cell, columnar cell, and oncotic variants of PTC and almost 80% of Warthin variants but only 27% of follicular variants. These data again show that the follicular variants appear to be distinct genetically from the oncotic variants.

Stage for stage, the prognosis of patients with the oncotic variant of PTC is similar to that of patients with conventional PTC. Oncotic variant of PTC has reduced capacity to uptake radioactive iodine and is therefore less responsive to radioactive iodine therapy.75,79–80

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Figure 6. High-power view of nuclear cytology in a case of oncocytic follicular variant of papillary thyroid carcinoma (hematoxylin-eosin, original magnification ×200).

Figure 7. A, Low-power view of Warthin-like variant of papillary thyroid carcinoma (hematoxylin-eosin, original magnification ×50). B, High-power view showing classic papillary carcinoma nuclei in Warthin-like variant (hematoxylin-eosin, original magnification ×200).

Figure 8. A, Tall cell variant of papillary thyroid carcinoma (hematoxylin-eosin, original magnification ×200). B, Tall cell variant of papillary thyroid carcinoma showing extrathyroidal spread (hematoxylin-eosin, original magnification ×100). C, Spindle cell/squamous transformation in tall cell variant of papillary thyroid carcinoma (hematoxylin-eosin, original magnification ×200).
Recently, Mai et al\(^{82}\) examined 19 cases of encapsulated Hürthle cell neoplasms with papillary architecture that lacked nuclear features of papillary carcinoma. In their study, they identified proliferative activity in the neoplastic cells associated with the papillary architecture and felt the papillary changes were part of the lesion and not a degenerative process as described in some oncocyti tumors. All 19 of their patients were free of disease with follow-up (1–19 years after diagnosis). This group believes the term papillary variant of oncocyti (Hürthle cell) adenoma should be used to describe these overall benign-acting oncocyti lesions.\(^{82}\)

**Warthin-like Variant of PTC**

The Warthin-like PTC is a variant that is characterized by a papillary growth of oncocyti cells with classic nuclear features of PTC and an associated brisk lymphoplasmacytic infiltrate in the papillary stalks.\(^{83,84}\) The variant is so-named because of its close resemblance to parotid gland Warthin tumor (Figure 7, A and B). These tumors often have an associated chronic lymphocytic thyroiditis with oxyphilia in the background thyroid. The differential diagnosis includes the tall cell variant of PTC; however, despite the oncocyti cells, the cells are not twice as tall as they are wide. The prognosis of this lesion is similar to that reported with typical PTC. We have seen unusual cases of Warthin-like PTC transition to tall cell PTC at its invasive edge and then invade into extrathyroidal soft tissues. The clinical behavior of such lesions (based on anecdotal observations) seems to more closely follow that of Warthin-like papillary carcinoma than the tall cell phenotype.

Trovisco et al\(^{85}\) identified BRAF mutations in 75% of Warthin-like PTCs versus 46% of usual-type PTCs. In contrast though, Sargent et al\(^{86}\) observed BRAF mutations only rarely in a variety of papillary carcinomas arising in a background of chronic lymphocytic thyroiditis and not in Warthin variant.

**Tall Cell Variant of PTC**

In 1976 Hawk and Hazard\(^{86}\) described a variant of PTC that was characterized by carcinoma cells with classic papillary carcinoma nuclei but abundant cytoplasm in which the cells were 3 times as tall as they were wide. The distinction between this tall cell variant and the usual variant of papillary carcinoma proved to be important because the tall cell variant showed a more aggressive behavior and because tumors were large, more often showed extrathyroidal extension, and showed a propensity for vascular invasion\(^{86,87}\) (Figure 8, A and B). The cells in this tumor are described as tall, with the most recent definition indicating their height is at least 3 times their width and most of them have an eosinophilic cytoplasm. However, the tumor cells are less granular than Hürthle cells. There has been debate about the amount of tall cells needed to make a diagnosis of tall cell variant of PTC. We prefer a diagnosis of tall cell variant when tumors show more than 70% tall cells in their study without extrathyroidal extension with usual-type PTC. In their study, they observed that tall cell variants even without the adverse feature of extrathyroidal extension were more likely to develop lymph node and distant metastases and they concluded tall cell variant of PTC without extrathyroidal extension is a more aggressive variant of papillary carcinoma independent of age, gender, and tumor size. Adeniran et al\(^{82}\) identified BRAF mutations more commonly than RET/PTC and RAS mutations in tall cell variants of PTC.

**Oncocyti Variant of Medullary Thyroid Carcinoma**

Some medullary thyroid carcinomas are composed of large cells with finely granular cytoplasm and superficial study can suggest a Hürthle cell lesion.\(^{91}\) However, the nuclear characteristics are different because most medullary carcinomas have uniform, small nuclei unlike the pleomorphic nuclei in the Hürthle cell tumors. The cytoplasmic granularity is less pronounced in medullary lesions, and the latter rarely demonstrate intense eosinophilia. In any questionable case, of course, immunohistochemical staining for calcitonin and thyroglobulin will aid in reaching the correct diagnosis.

**Granular Cell Tumor**

Granular cell tumor is a rare tumor most likely of Schwann cell origin. Approximately 50% of the cases have been reported in the head and neck region. They can occur in other organs, including respiratory tract, gastrointestinal tract, genitourinary tract, vulva, and breast. Rarely these tumors can occur in thyroid or adjacent to the thyroid and clinically present as thyroid masses.\(^{92}\) Most reported tumors in the thyroid occur in women, behave in a benign fashion, and can be treated with lobectomy.

**FINE-NEEDLE ASPIRATION BIOPSY OF HÜRTHLE CELL LESIONS**

Hürthle cells of the thyroid in cytologic specimens appear as large polygonal cells with ample eosinophilic granular cytoplasm and central or occasionally eccentrically placed nuclei containing prominent nucleoli. The cell borders appear sharply demarcated and one may see empty space between 2 Hürthle cells similar to “windows” seen in mesothelial cells. Intranuclear grooves can be seen in Hürthle cells in Papaineloset-stained smears and monolayer preparations\(^{93,94}\) (Figure 9, A and B). Hürthle cells can be a prominent component in fine-needle aspiration (FNA) specimens from Hürthle cell adenomas and carcinomas, Hürthle cell nodules in Hashimoto thyroiditis, adenomatoid nodules with Hürthle cell metaplasia, and nodules arising in a background of Graves disease.\(^{95}\) Because Hürthle cells can be present in both nonneoplastic and neoplastic thyroid lesions it can be diagnostically challenging to differentiate between these two in thyroid FNA specimens.\(^{95,96,97}\)

**Nonneoplastic Hürthle Cell Lesions**

Hyperplastic/adenomatoid nodules in multinodular goiter and Hashimoto thyroiditis can show a preponderance of Hürthle cells. In the former, the background usually shows watery colloid and macrophages; however, of utmost importance is the presence of a second cell population of small follicular cells containing scant cytoplasm...
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Figure 9. A, Papanicolaou-stained smear showing a monotonous population of Hurthle cells arranged in loosely cohesive groups consistent with Hurthle cell neoplasm (original magnification ×200). B, Papanicolaou-stained smear showing Hurthle cell with oncocytic cytoplasm, prominent nucleoli, and even intranuclear grooves (original magnification ×500).

and small nuclei with dense chromatin.98,99 The Hurthle cells may demonstrate intranuclear grooves and even focal nuclear chromatin clearing; however, the nuclei are round in shape with prominent nucleoli and other features of papillary carcinoma are not seen.99 The FNA specimens from a Hurthle cell nodule in Hashimoto thyroiditis usually show Hurthle cells arranged in sheets, follicular groups, and singly scattered cells. The latter are seen scattered in the background or arranged in loosely cohesive lymphoid follicles. The most important feature is that the lymphocytes are also seen percolating among the majority of cell groups.100–102 In our experience this is an important feature that distinguishes neoplastic versus nonneoplastic Hurthle cell lesions arising in a background of chronic lymphocytic thyroiditis. Hurthle cells in Hashimoto thyroiditis can display nuclear atypia that mimics papillary cancer, that is, intranuclear grooves, nuclear chromatin clearing, and rarely intranuclear inclusions. One must be aware of this and exercise caution in diagnosing PTC in Hashimoto thyroiditis. Usually the Hurthle cells with these atypical nuclei still maintain a round shape with smooth nuclear membrane and prominent nucleoli. Some authors have suggested that immunostains for cytokeratin 19, HBME-1, and galectin-3 can be helpful in solving this diagnostic dilemma; however, others have shown that follicular and Hurthle cells in Hashimoto thyroiditis can show positive immunostaining with all the previously mentioned markers.103

**Hürthle Cell Neoplasm**

Fine-needle aspiration cytology cannot differentiate between Hurthle cell adenoma and carcinoma because this distinction is dependent on demonstration of capsular and/or vascular invasion by histopathologic examination. Therefore, cytopathologists can only render a diagnosis of Hurthle cell lesion/neoplasm. These specimens demonstrate a monotonous population of Hürthle cells comprising more than 90% of the specimen. The cells are seen arranged in sheets, follicular groups, and singly scattered cells. Some authors have suggested that on the basis of nuclear atypia such as prominent nucleoli, high nuclear-cytoplasmic ratio, and nuclear pleomorphism one can differentiate between Hürthle cell adenoma and carcinoma; however, others have refuted these observations. It has been shown that transgressing vessels and intracytoplasmic lumina are more commonly seen in neoplastic rather than nonneoplastic lesions.93,104 Others have shown that transgressing vessels are a more reliable criterion for the diagnosis of Hürthle cell neoplasm as compared with intracytoplasmic lumina.93 In our experience, monotonous population of Hürthle cells comprising more than 90% of the specimen is a reproducible and reliable criterion for the diagnosis of Hürthle cell neoplasm.

**FNA Biopsy of Papillary Hürthle Cell Carcinoma With Lymphocytic Stroma**

(“Warthin-like Tumor” of the Thyroid)

This variant of papillary cancer displays peculiar morphology that closely resembles the papillary cystadenoma lymphomatosum or “Warthin tumor” of the salivary gland. It is usually seen in the thyroids affected by chronic lymphocytic thyroiditis. The key histologic features include oncocytic follicular epithelium arranged in papillae with nuclear features of papillary carcinoma and a brisk infiltrate of lymphocytes and plasma cells in the cores of papillary stalks. The FNA specimens from such tumors show oncocytic cells with nuclear features of papillary carcinoma and an admixture of lymphocytes. The FNA specimens and the histologic sections from Warthin-like papillary carcinoma can pose difficulties in distinguishing these lesions from florid chronic thyroiditis itself, Hürthle cell nodules in chronic lymphocytic thyroiditis, Hürthle cell tumors, tall cell variant of papillary carcinoma (PTC), and oncocytic variant of medullary carcinoma.84,105

The biologic behavior of these Warthin-like tumors is similar to usual papillary carcinoma when compared for tumor size and stage.

**CYTOLOGY OF TALL CELL VARIANT OF PAPILLARY CARCINOMA**

Cytology specimens of this tumor usually show elongated cells with sharp cytoplasmic borders, granular eosinophilic cytoplasm, and variably sized nuclei with nuclear features of papillary carcinoma. The nuclear features of papillary carcinoma are usually abundant in aspirates of tall cell variant as compared with that of classic PTC. Thus, nuclear grooves and inclusions are readily identifi-
able. Some authors have reported presence of intraepithelial neutrophils in aspirates from cases of tall cell variant of PTC. This tumor can be confused with tall cell carcinoma on cytology due to cytoplasmic eosinophilia; however, the nuclear features should help in differentiating between these two tumors.

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