Fine Needle Aspiration Cytology of Endocrine Tumors

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Abstract Fine-needle aspiration biopsy (FNAB) has proved to be an excellent diagnostic tool in the initial management of various lesions affecting endocrine organs. Many studies have attested to its high sensitivity and specificity in diagnosing endocrine tumors, especially that of thyroid gland. However, as with other diagnostic tests its effectiveness is highly dependent upon the expertise of the operator performing the procedure, adequacy of the specimen, and interpretation of the cytomorphologic features. This chapter will address both old and new of the endocrine cytology: including brief description of cytologic features and differential diagnosis of various endocrine lesions and new techniques that have shown promise in their diagnosis

Keywords Endocrine • Cytology • FNA • Immunohistochemistry • Molecular markers

Introduction

During the past decade fine-needle aspiration (FNA) has become an essential tool in the management of common endocrine lesions. This chapter describes and illustrates the cytomorphologic features of the lesions affecting thyroid, parathyroid, pancreas, and adrenal. For the common lesions such as thyroid the cytological features are described and the differential diagnoses are discussed in detail. The discussion also includes an assessment of modern techniques such as immunohistochemistry and molecular analyses with emphasis on their validity for FNA samples as well as the pitfalls that are encountered in their use.

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Cytopathology of Thyroid Gland

Thyroid nodules are common; they are often seen in women and a great majority are benign. Fine-needle aspiration (FNA) is considered an essential tool in providing a rational approach to the clinical management of these nodules. The results of FNA can determine whether a thyroid nodule should be followed clinically or undergo surgical removal [1, 2].

FNA Indications, Procedure, Specimen, and Classification

A palpable thyroid nodule is a candidate for FNA and further evaluation should be performed to determine if an FNA is needed. Thyroid nodules measuring 1.0–1.5 cm in dimension can be detected by palpation and are therefore clinically significant. However, thyroid nodules even though measuring >1.0 cm may not be readily palpated due to their location in the thyroid gland [2]. These and nodules measuring >1.0 cm are usually found during radiologic evaluation of the head and neck for non-thyroidal lesions. Thyroid nodules can be biopsied by palpation and/or under ultrasound guidance; the latter is becoming the method of choice since it provides precise information regarding the location, size, and structure (solid vs. cystic) of the nodule and is highly effective in getting an adequate sample for cytologic interpretation [3].

Thyroid FNA specimens can be prepared by making air-dried and alcohol fixed smears for staining with Romanowsky (Diff-Quik®, Wright-Giemsa) and Papanicolaou stains, respectively. The smears can be processed alone or with a liquid-based preparation or cell block [1]. Liquid-based preparations can be utilized either alone or as an adjunct to the smears [1].

The main purpose of the fine-needle aspiration (FNA) is to provide a rational approach for the management of

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thyroid nodules and determine the correct surgical procedure when surgery is needed. Similar to other clinical tests in medicine, it is often expected that thyroid FNA results should demonstrate high degree of sensitivity and specificity. Therefore, it is prudent that thyroid FNA reporting should be close to uniform among pathologists to pave the path for rational management strategies and avoid confusion among clinicians, thus leading to optimal care of thyroid nodules [4].

At present several classification schemes have been proposed by various authors based on anecdotal/institutional experiences and clinical organizations including Papanicolaou Society, American Thyroid Association, and American Association of Clinical Endocrinologist [2, 4–6] (Table 1). Each of these reporting strategies claims to increase the diagnostic accuracy resulting in highest possible predictive value for a positive result.

Table 1 Thyroid FNA classification schemes

Papanicolaou Society of Cytopathology Task Force on Standards of Practice – 1997	1. Inadequate/unsatisfactory 2. Benign 3. Atypical cells present 4. Suspicious for malignancy 5. Malignant
American Thyroid Association (2006)	1. Inadequate 2. Malignant 3. Indeterminate ■ Suspect for neoplasia ■ Suspect for carcinoma 4. Benign
American Association of Clinical Endocrinologists & Associazione Medici Endocrinologi – 2006	1. Benign 2. Malignant or suspicious 3. Follicular neoplasia 4. Non-diagnostic or ultrasound Suspicious
NCI Thyroid FNA Consensus Conference – 2007	1. Benign 2. Follicular lesion of undermined significance. 3. Neoplasm (follicular or Hurthle) 4. Suspicious for malignancy 5. Malignant 6. Non-diagnostic

It has been shown that the predictive value of a positive result is highest with a reporting scheme using 4–5 categories. Thus, most studies favor a tiered system for classifying thyroid FNA, based upon risk of malignancy for each diagnostic category [7].

Thyroid FNA Diagnostic Categories Including Cytomorphology of Various Thyroid Lesions

Benign

This category implies low risk of neoplasm/malignancy, i.e., >1%. It includes the diagnostic terms such as *nodular goiter, hyperplastic/adenomatoid nodule in goiter, and chronic lymphocytic thyroiditis*. Patients with a benign nodule are usually followed by clinical and periodic ultrasound examination; some patients may undergo repeat FNA due to enlargement of the nodule [2].

The FNA specimen from a goitrous nodule shows (depending upon the preparation method) copious watery colloid in the background, small round to oval shaped follicular cells with dark nuclei with even chromatin pattern arranged in monolayer sheets, follicular groups, or as single cells [8, 9]. Macrophages are usually present and their number depends upon the presence or absence of degenerative changes or a cystic component in the nodule [9, 10].

The aspirates from a hyperplastic/adenomatoid nodule tend to be more cellular and contain an admixture of follicular cells and oncocytic cells arranged in monolayer sheets in a background of watery colloid and macrophages [9–11]. Hyperplastic nodules can also show a dominant papillary growth pattern and give rise to well-formed papillae in FNA specimens; however, most specimens contain oncocytic follicular cells with round nuclei, prominent nucleoli, and even chromatin pattern (Fig. 1).

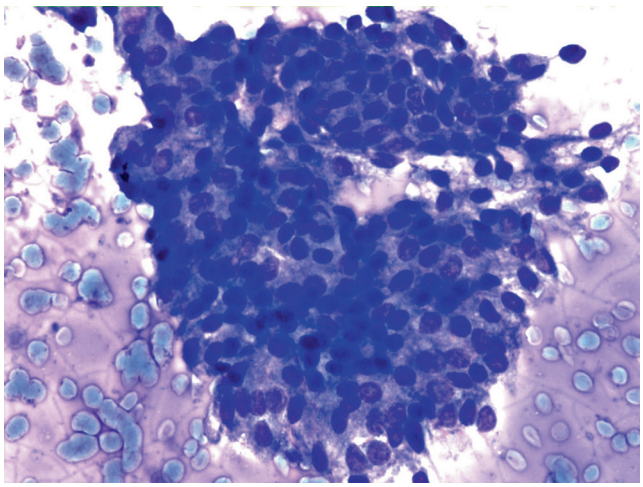


Fig. 1 Fine-needle aspiration smear of a hyperplastic nodule showing follicular cells arranged in loosely cohesive group in the background of watery colloid with a typical "chicken wire artifact" (Diff-Quik® stain, 60×)

The FNA specimens from a nodule arising in Graves' disease (usually hypofunctioning nodules undergo FNA) are usually cellular, show features similar to hyperplastic goiter with minimal colloid and may contain few lymphocytes and oncocytic cells. Rarely the follicular cells may display focal nuclear chromatin clearing and intranuclear grooves; however, other major diagnostic nuclear features of papillary carcinoma are not seen [12–15].

The FNA specimens from nodules arising in chronic lymphocytic thyroiditis contain oncocytes (Hürthle cells),

follicular cells, lymphocytes, and few plasma cells in a background of scant colloid. The lymphocytes are usually seen in the background, percolating between cell groups and rarely as intact lymphoid follicle. The lymphocytes seen within the cell groups can be crushed due to mechanical force of smearing or centrifugation and lead to formation of "lymphocytic tangles." The oncocytes may display nuclear atypia and similarly follicular cells may show some chromatin clearing and intranuclear grooves. An extensive lymphocytic infiltrate can appear monotonous and mistaken for malignant lymphoma arising in lymphocytic thyroiditis [16–19]. Similarly, there may be a preponderance of oncocytic cells, which can lead to a diagnosis of oncocytic follicular neoplasm.

Follicular-Patterned Neoplasms

Thyroid (FNA) cannot distinguish between benign and malignant non-papillary follicular and oncocytic follicular (Hürthle cell) lesions, since both benign and malignant neoplasms demonstrate similar cytomorphology [20]. Often these lesions are diagnosed as either follicular lesion of undetermined significance, suspicious for follicular neoplasm, or follicular neoplasm.

The diagnostic term follicular lesion of undetermined significance represents a heterogeneous category, which reflects the difficulty in the cytologic diagnosis of the follicular lesions of thyroid. It includes cases in which the cytomorphologic findings are not representative of a benign lesion such as hyperplastic/adenomatoid nodule; yet the degree of cellular or architectural atypia is not sufficient to render the diagnosis of "follicular neoplasm" or "suspicious for follicular neoplasm/malignancy" that cannot be classified as either benign or follicular neoplasm. Risk of malignancy for this diagnosis has been reported as 10–15%, and it has been shown that these patients can benefit from repeat FNA and correlation with clinical and radiologic findings [1, 21].

The diagnostic terms follicular neoplasm/follicular neoplasm with oncocytic features (AKA Hürthle cell neoplasm)/suspicious for follicular neoplasm encompasses both benign and malignant tumors; i.e., follicular adenoma and carcinoma, and oncocytic follicular adenoma and carcinoma. The cytologic diagnosis of "neoplasm" reflects the limitations and is the "gray zone" of thyroid cytology [22, 23]. The diagnosis of follicular carcinoma is only possible by demonstration of capsular and/or vascular invasion in histologic preparations, since the FNA samples the center of the nodule and not the capsule, a definitive diagnosis of the invasive nature of the lesion is not possible. Several authors have shown that, at most, only 20–30% of cases diagnosed as "follicular neoplasm" are diagnosed as malignant on histological examination and the rest are either follicular adenomas or cellular adenomatoid nodules, i.e., benign [21, 24].

The FNA of a follicular neoplasm is usually hypercellular and show a monotonous population of either follicular or oncocytic follicular cells with minimal or absent background colloid. The cells can be seen as three dimensional groups or microfollicles with prominent nuclear overlapping and crowding [25] (Fig. 2). Random nuclear atypia is also commonly observed in oncocytic follicular (Hürthle cell) lesions; this can be seen in the form of nuclear enlargement, multinucleation, cellular pleomorphism, and prominent nucleoli. Some authors have reported the presence of intracytoplasmic lumens and transgressing vessels in FNA specimens of neoplastic oncocytic follicular (Hürthle cell) lesions [26].

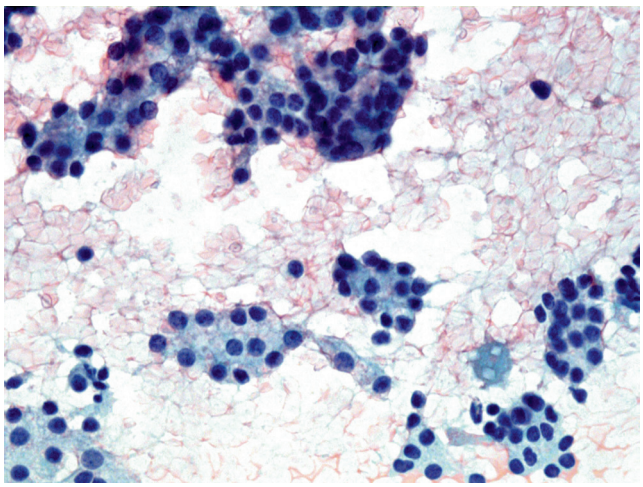


Fig. 2 Fine-needle aspiration smear showing a monotonous population of follicular cells arranged in microfollicles. This case was diagnosed as follicular neoplasm and the subsequent surgical excision was diagnosed as follicular adenoma (Papanicolaou stain, 40×)

Malignant

The well-differentiated thyroid carcinomas are the most common form of malignant thyroid tumors that behave in an indolent manner and have an excellent prognosis. They commonly occur in young adults, whereas, the less differentiated and anaplastic tumors of the thyroid are prevalent in older age [27].

Papillary Thyroid Carcinoma (PTC) and Its Variants

Papillary carcinoma is the most common (up to 80% of all thyroid malignancies) form of thyroid malignancy in non-endemic goiter regions [27].

The cytologic diagnosis of PTC is based on characteristic nuclear morphology regardless of cytoplasmic features, growth pattern, special stains, and immunohistochemical markers. This holds true for a majority of cases of PTC; however, some variants of PTC may be difficult to diagnose [28, 29]. The FNA specimen of PTC is usually cellular and shows tumor cells arranged in papillary groups, three-dimensional clusters, or as single cells in a background of watery or thick "ropy" colloid, nuclear or calcified debris, macrophages, and stromal fragments.

The individual tumor cells are enlarged, elongated, i.e., oval in shape with eosinophilic cytoplasm (cytoplasmic eosinophilia is common in Romanowsky stained preparations but is usually indistinct in alcohol fixed Papanicolaou stained preparations and liquid-based preparations) [8]. The nuclei show elongation, membrane thickening, chromatin clearing, grooves, and inclusions. The intranuclear inclusions may be scarce in monolayer preparations (Fig. 3). The nucleoli are usually small and eccentric; however, rare oncocytic variants of papillary thyroid carcinoma can demonstrate prominent nucleoli/macronucleoli. Intranuclear grooves and inclusions can be seen in other benign and malignant conditions of thyroid [30, 31].

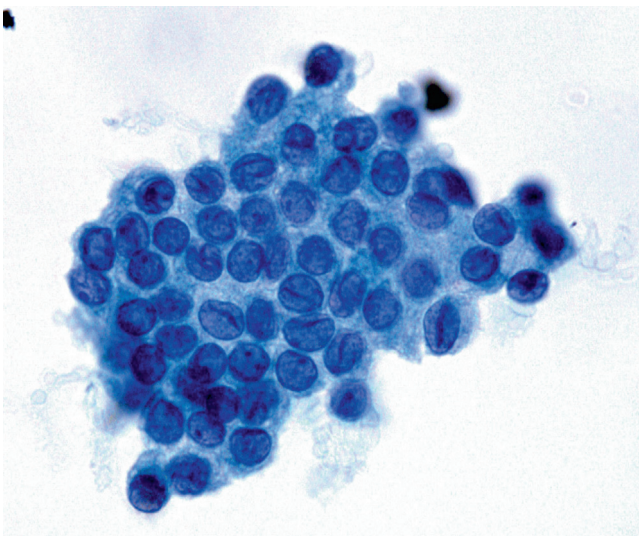


Fig. 3 A case of papillary thyroid carcinoma demonstrating typical nuclear features – nuclear elongation, chromatin clearing, intranuclear grooves and inclusions (Papanicolaou stained Thin-Prep preparation, 60×)

The FNA specimens from a ***follicular variant of papillary carcinoma (FVPTC)*** show enlarged follicular cells arranged in monolayer sheets and follicular groups in a background of thin and thick colloid. The individual tumor cells show nuclear elongation, chromatin clearing, and thick nuclear membranes; however, nuclear grooves and inclusions are rare. Thus, a majority of cytologic samples of FVPTC are diagnosed as suspicious for PTC [32].

The cytologic samples from ***tall cell variant of papillary carcinoma*** contain elongated cells with sharp cytoplasmic borders, granular eosinophilic cytoplasm, and variably sized nuclei with nuclear features of papillary carcinoma [33]. It has been shown that intranuclear grooves are readily found in specimens from this tumor; characteristic "soap bubble" like inclusions has been reported in this variant of papillary carcinoma [33].

Medullary Thyroid Carcinoma

Medullary thyroid carcinoma (MTC) originates from C cells of the thyroid and constitutes about 10% of all malignant thyroid tumors. This tumor also shows multiple growth patterns and variable cytomorphology [34].

Thus FNA specimens from MTC display a spectrum of morphologic patterns. They tend to be cellular and comprised of round-to-oval cells arranged mostly as single cells or loosely cohesive groups. The cytoplasm of the tumor cells shows distinct granules (calcitonin granules highlighted by immunostains) with eccentric nuclei, i.e., "plasma cell like/plasmacytoid" appearance to the tumor cells (Fig. 4). The nuclear chromatin is similar to that seen in other neuroendocrine tumors, i.e., "salt and pepper type." Intranuclear inclusions and multinucleated cells have been reported, thus this tumor being a great mimicker of other tumors of thyroid. The tumor cells can also assume a "spindle shape" and appear mesenchymal in origin. Amyloid may be observed as acellular material alone or in close association with tumor cells and can be distinguished from the thick colloid of papillary carcinoma by performing a Congo red stain. The diagnosis of MTC can

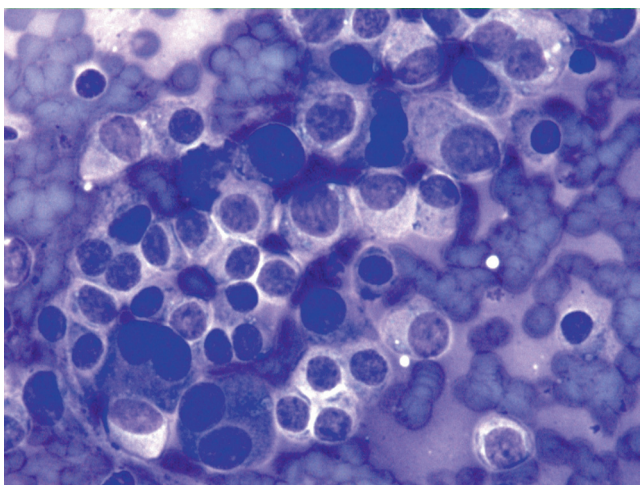


Fig. 4 A case of medullary carcinoma showing plasmacytoid cells with granular cytoplasm (Diff-Quik® stain, 60×)

be confirmed by performing immunostains for calcitonin and thyroglobulin [35, 36]. In a limited cellularity specimen it is advisable to recommend serum calcitonin levels to confirm the diagnosis of medullary carcinoma determination rather than performing immunostains [2, 6].

Anaplastic Carcinoma

Anaplastic carcinoma of the thyroid is one of the most clinically aggressive and fatal human tumors. The aspirates from anaplastic carcinoma usually do not pose any diagnostic difficulties; they can be readily classified as malignant due to extreme cellular pleomorphism, necrosis, and obvious malignant features [37].

Role of Special Studies in the Diagnosis of Thyroid Tumors in Cytologic Specimens

Immunohistochemistry

All follicular derived thyroid lesions, i.e., benign and malignant, express transcription factor (TTF-1) and thyroglobulin. This immunopanel is helpful in differentiating primary vs. secondary tumors of the thyroid [38]. The diagnosis of medullary carcinoma can be established in FNA specimens by performing immunostains for calcitonin and calcitonin gene related peptide (CGRP). Medullary carcinoma also stains positive for monoclonal carcinoembryonic antigen (CEA), chromogranin, synaptophysin, and TTF-1 [35, 39].

The use of various immunohistochemical markers in cytologic samples to differentiate papillary carcinoma from other follicular derived lesions of the thyroid have been explored by many authors. The immunopanel comprising of cytokeratin-19, HBME-1, and Galectin-3 have shown acceptable sensitivity and specificity, however, one must be aware of the fact that benign thyroid epithelium in chronic lymphocytic thyroiditis and post-FNA reactive foci can stain positive for both CK-19 and Galectin-3. This can lead to false positive diagnosis of malignancy [40–42]. Therefore, results of these stains must always be interpreted with care and correlated with the basic cytomorphology.

Molecular Genetics/Diagnosis

In the past decade much has been published on the role of various biologic events and genetic determinants in the pathogenesis of various thyroid tumors.

RET/PTC: Rearrangements of RET gene, known as RET/PTC have been identified in papillary carcinoma of thyroid [43]. RET/PTC 1 and 3 are the most common forms that occur in sporadic papillary carcinoma [44]. The prevalence of RET/PTC in papillary carcinoma varies significantly among various geographic regions [43, 45, 46]. Several authors have investigated the expression of RET/PTC rearrangements in thyroid aspirates to establish the diagnosis of papillary thyroid carcinoma [47, 48]; however, RET/PTC expression can also occur in some benign lesions, including hyalinizing trabecular neoplasm [49], chronic lymphocytic thyroiditis [50], hyperplastic nodules, and follicular adenoma [51, 52]. Thus, employing only RET/PTC analysis of FNA specimen to establish the diagnosis of PTC does not appear to be reliable.

BRAF*:* 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 [53, 54, 55]. These mutations are independent of RET/PTC translocations or RAS mutations. BRAF mutational analysis of FNA samples has been shown to be of value in the diagnosis of papillary thyroid carcinoma. Some authors have suggested that since BRAF mutations, RET/PTC rearrangements, and RAS mutations are independent of each other, it may be helpful to analyze multiple markers in a given thyroid FNA specimen to establish the diagnosis of PTC [48].

DNA Microarray Analysis: Recently DNA microarray analysis of the thyroid FNA samples has been shown to successfully distinguish between the majority of benign and malignant thyroid lesions. It has been shown that based on these analyses FNA cohort could be separated into three clusters: malignant, benign, and indeterminate by unsupervised hierarchical cluster analysis [56].

Cytopathology of Parathyroid Gland

Most parathyroid lesions are not palpable; it is unusual to directly biopsy by FNA a parathyroid tumor. However, on occasion, parathyroid lesions present clinically as thyroid nodules or are large enough to be clinically evident. In such cases, an FNA may sample a proliferative parathyroid lesion [57]. With the advent of the image-guided fine-needle aspiration technique the number of FNA of neck masses is increasing, and so is the number of aspirated normal and/or neoplastic parathyroid tissue [57, 58]. Various studies have emphasized upon the difficulties in differentiating the parathyroid lesions from the

neoplastic and non-neoplastic diseases of the thyroid in cytology specimens [59, 60]. The possibility of the ectopic location of parathyroid gland, including intrathyroidal location, clinical similarity between the parathyroid and thyroid lesions, overlap in their cytomorphology, and coexistence of pathology in both glands undoubtedly contribute to the misinterpretation of the fine needle aspirates [61]. Parathyroid lesions in the fine needle aspirates are most commonly confused with the thyroid neoplasms, papillary, follicular or Hürthle cell, adenomatoid thyroid nodules, or with lymphocytic thyroiditis. This is due to the presence of tissue fragments with papillary architecture, epithelial cells arranged in microfollicular pattern, colloid like material in the background, and due to the presence of oxyphil cells and naked nuclei of chief cells resembling Hürthle cells and lymphocytes, respectively [61, 62].

Although the literature dealing with the parathyroid FNA is sparse, most authors emphasize that there is no single diagnostic criterion that helps to reliably differentiate parathyroid lesions from those of thyroid, but rather a combination of cytomorphologic features should be used. Most helpful might be the presence in the parathyroid aspirates of three-dimensional fragments, naked nuclei admixed with cohesive cell clusters, (Fig. 5) nuclear overlapping, nuclear molding, and presence of mast cells [62]. In addition to cytomorphology, immunoperoxidase staining for the parathyroid hormone and thyroglobulin, chromogranin, and assays of PTH level of the aspirated fluid have shown to be of value in the cytologic diagnosis of parathyroid lesions [60, 62].

Cytopathology of Adrenal Gland

Fine-needle aspiration (FNA) is considered by many as the procedure of choice in the diagnosis of adrenal gland lesions [63, 64]. The possible causes for performing adrenal gland FNA include adrenal mass incidentally found on abdominal imaging, adrenal mass responsible for patients symptoms and altered adrenal function and adrenal mass encountered during the staging workup in a patient with known history of malignancy. However, the most important reason for performing adrenal FNA is to distinguish between primary and metastatic adrenal tumors [63, 64].

Benign adrenal cortical nodules are common and account for approximately 33% of adrenal lesions undergoing FNA. Though size is an important criterion for distinguishing between benign and malignant adrenal cortical nodules, one must be aware of the fact that metastatic nodules can also measure 1 cm or less [63, 65]. The most important criterion in making a diagnosis of neoplasm of adrenocortical origin is to be 100% sure that the FNA needle is within the nodule, since by morphology normal adrenocortical tissue is indistinguishable from the adrenocortical adenoma or adrenocortical tumors of undermined malignant potential [64]. The FNA specimens from adrenal tumors are usually cellular and show tumor cells in a lipid rich background (best seen in Diff-Quik stained slides). The individual cells display central or eccentrically placed nuclei with evenly dispersed chromatin and small nucleoli (Fig. 6). The cytoplasm is usually foamy and ill defined and a majority of cells can appear as stripped nuclei. The cells can occur as large cohesive fragments or singly scattered cells; some specimen can

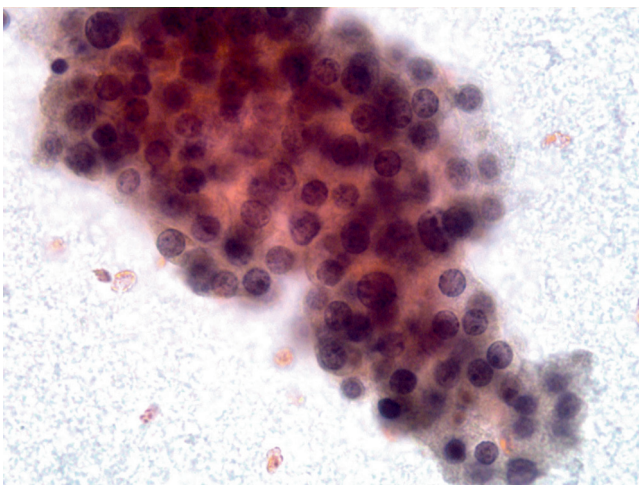


Fig. 5 Fine-needle aspiration of a parathyroid lesion demonstrating a monotonous population of cells arranged in cohesive group; notice the sharp cytoplasmic borders and clear cytoplasm. The PTH analysis of the aspirate confirmed the parathyroid origin. (Papanicolaou stained ThinPrep preparation, 60×)

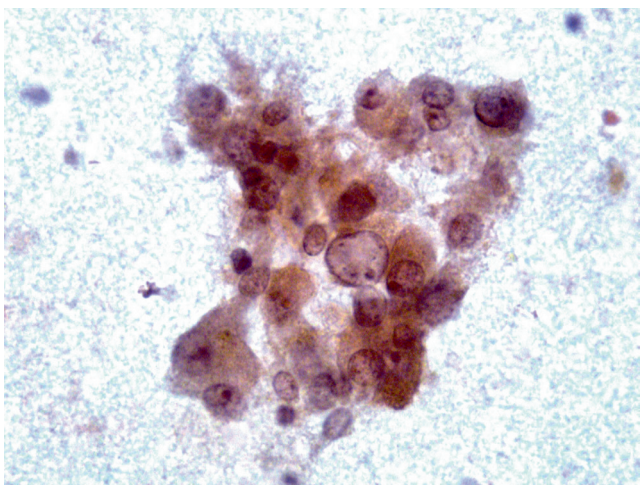


Fig. 6 Fine-needle aspiration of an adrenal cortical adenoma showing adrenal cortical cells with granular cytoplasm, round nuclei with prominent nucleoli (Papanicolaou stained Millipore® filter preparation, 60×)

show mostly singly scattered cells which can occur as a function of smearing technique or in large adrenal tumors with necrosis [63, 65, 66].

The differential diagnosis of FNA specimens from adrenocortical tumors includes renal cell carcinoma and metastatic mucinous adenocarcinoma. It is a challenge in cytology practice to differentiate between aspirates from renal cell carcinoma and adrenocortical tumors. Specimens from renal cell carcinoma usually lack lipid-rich background; however, in our practice, it is important to obtain enough material for immunostains to differentiate between these two entities. The aspirates from metastatic adenocarcinoma are mainly comprised of large cohesive fragments of tumor cells with marked nuclear pleomorphism with background necrosis [67, 68]. Mucicarmine stain can be helpful in the diagnosis of adenocarcinoma. Immunostains for CK-20, CK-7, CEA, EMA, Inhibin, and Calretinin, can be helpful in differentiating between primary adrenocortical tumors and metastatic adenocarcinoma [69, 70].

Rarely one may also encounter normal hepatocytes in FNA samples of right adrenal gland. Before making the diagnosis of accidental aspiration of normal liver, it is important to know that some adrenal tumors can show prominent oncocytic features. Normal hepatocytes are usually polygonal in shape with distinct cell borders, granular cytoplasm, and prominent nucleoli [70, 71].

There have been few reports describing the FNA cytology of pheochromocytoma. The cytology specimens are usually cellular and show many single cells and few tissue fragments. The latter may consist of a capillary rich stroma. The tumor cell cytoplasm is usually fragile leading to abundant bare nuclei; if present, the cytoplasm can show metachromatic granules, especially in Diff-Quik stained smears. Nuclear pleomorphism is readily evident (Fig. 7); usually the nuclei show salt and pepper chromatin with occasional intranuclear inclusions. In some cases one may also observe a variable number of ganglion-like cells [72, 73].

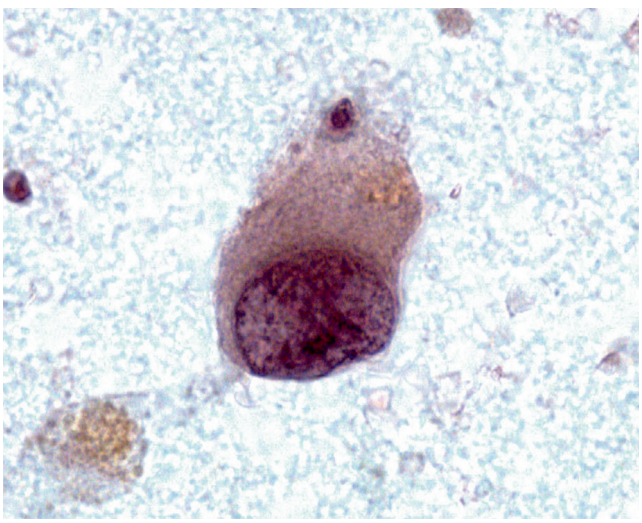


Fig. 7 Fine-needle aspiration specimen of a pheochromocytoma containing tumor cell displaying marked nuclear pleomorphism (Papanicolaou stained Millipore® filter preparation, 100×)

Cytopathology of Pancreatic Neuroendocrine Tumors

Pancreatic endocrine tumors (PET) account for approximately 1–2% of all neoplasms in the pancreas [74]. They may manifest clinically as functional tumors elaborating a variety of hormones or be nonfunctional. The nonfunctional tumors are detected as incidental findings on abdominal imaging or the patient may present with liver metastasis. The pancreas and the liver are amenable to percutaneous CT-guided fine-needle aspiration and fine-needle is often the first diagnostic test in an attempt to ascertain the nature of a pancreatic mass. More recently, endoscopic ultrasound-guided fine-needle aspiration (EUS FNA) has largely replaced percutaneous FNA due to the added advantage of visualizing peripancreatic lymph nodes and the liver and obtaining aspiration biopsies in a single procedure, thus staging the patient with a suspected pancreatic neoplasm [74–76].

Cytomorphologic Characteristics of PET

The cytomorphologic characteristics of PET are not dissimilar to the carcinoid tumors found elsewhere in the body [75–78]. Aspirates are generally cellular, with the tumor cells dispersed singly as well as forming cohesive groups or rosette-like structures (Fig. 8). The nuclear features are typical of a neuroendocrine tumor, with eccentrically placed nuclei imparting a plasmacytoid appearance to the tumor cells with salt and pepper chromatin (Fig. 9). Cystic degeneration has been reported in less than 2% of all PET [79]. Oncocytic metaplasia [80], clear cell change in the cytoplasm of the tumor cells mimicking a metastatic clear cell carcinoma, has also been reported [81, 82].

Ancillary Studies in the Diagnosis of PET

Immunohistochemical markers of neuroendocrine differentiation (synaptophysin, chromogranin-A, and CD56)

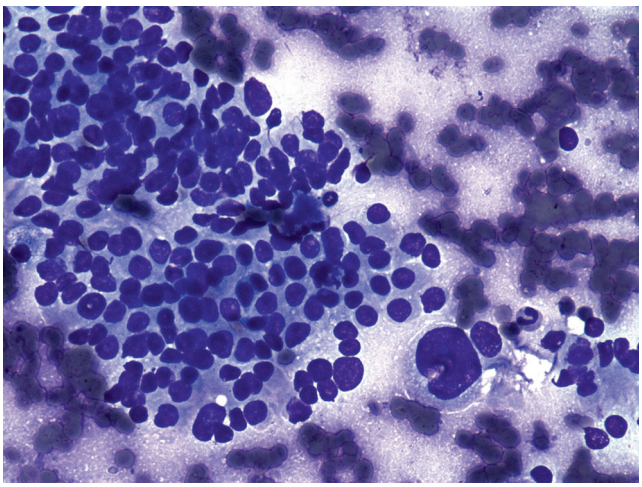


Fig. 8 Endoscopic-guided fine-needle aspiration specimen of a pancreatic endocrine tumor. The direct smear shows a group of uniform cells with round-to-oval nuclei arranged in an organoid pattern. Note the markedly enlarged cell in the *lower right* hand corner representing random nuclear atypia characteristic of endocrine tumors (Air-dried, Diff-Quik stained direct smear, 40×)

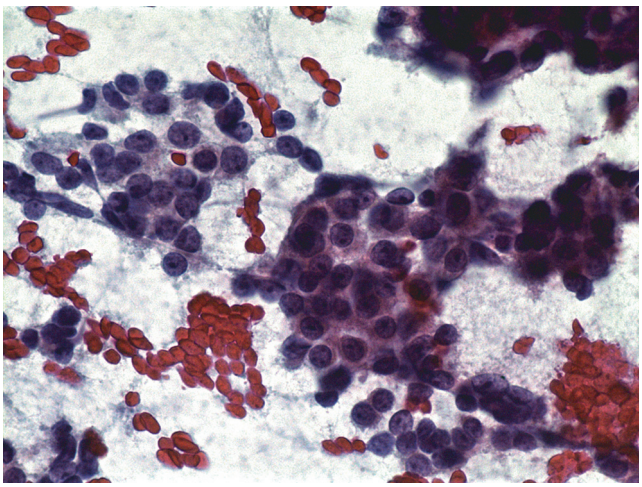


Fig. 9 Corresponding Papanicolaou stained smear from the above tumor exhibiting the characteristic nuclear characteristics of endocrine tumors. The tumor cells are arranged in a nested pattern with individual cells having moderate amount of cytoplasm. The chromatin pattern is finely granular and some of the nuclei do exhibit nucleoli (Alcohol fixed, Papanicolaou stained direct smear, 40×)

may be utilized on cell block material to confirm the diagnosis [75, 77, 83]. Two tumors that can be confused with PET on cytologic material include solid pseudopapillary tumor and acinar cell carcinoma of the pancreas. The former is characterized by the presence of tumor cells arranged in papillary fragments with fibrovascular cores. These tumors lack cytokeratin expression and stain strongly for ß-catenin, whereas PET shows diffuse and strong cytokeratin expression and stain negative for ß-catenin. Synaptophysin can be focally expressed in solid pseudopapillary tumor of the pancreas. Various authors have reported considerable overlap between immunohistochemical profile of PET and acinar cell carcinoma. Moreover, mixed acinar endocrine tumors of the pancreas make the differential diagnosis even more complicated. Skacel et al. [84] utilized a panel of immunohistochemical stains including synaptophysin, chromogranin-A, chymotrypsin, and α-1 antitrypsin to distinguish acinar cell from PET and concluded that the specificity of the neuroendocrine markers for PET and that of enzymatic markers for acinar cell carcinoma was too low to permit accurate classification using immunohistochemistry. One notable exception was the absence of chromogranin expression in acinar cell carcinoma and the expression of the same in about 60% of PET. Thus, caution should be exercised in distinguishing acinar cell carcinoma from PET in a limited cytology specimen [84, 85].

References

1. Baloch ZW, Cibas ES, Clark DP et al. The national cancer institute thyroid fine needle aspiration state of the science conference: a summation. *Cytojournal*. 2008;5:6.
2. Cooper DS, Doherty GM, Haugen BR et al. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid*. 2006;16:109–42.
3. Baskin HJ, Duick DS. The endocrinologists' view of ultrasound guidelines for fine needle aspiration. *Thyroid*. 2006;16:207–8.
4. American Association of Clinical Endocrinologists and Associazione Medici Endocrinologi medical guidelines for clinical practice for the diagnosis and management of thyroid nodules. *Endocr Pract*. 2006;12:63–102.
5. Guidelines of the Papanicolaou Society of Cytopathology for the Examination of Fine-Needle Aspiration Specimens from Thyroid Nodules. The Papanicolaou Society of Cytopathology Task Force on Standards of Practice. *Diagn Cytopathol*. 1996;15:84–9.
6. Baloch ZW, Livolsi VA, Asa SL et al. Diagnostic terminology and morphologic criteria for cytologic diagnosis of thyroid lesions: a synopsis of the national cancer institute thyroid fine-needle aspiration state of the science conference. *Diagn Cytopathol*. 2008;36:425–37.
7. Wang HH. Reporting thyroid fine-needle aspiration: literature review and a proposal. *Diagn Cytopathol*. 2006;34:67–76.
8. Kini SR. *Guides to Clinical Aspiration Biopsy Thyroid*. 2nd ed ed. New York, NY: Igaku-Shoin; 1996.
9. Layfield LJ, Wax T, Jones C. Cytologic distinction of goiterous nodules from morphologically normal thyroid: analyses of cytomorphologic features. *Cancer*. 2003;99:217–22.
10. Baloch ZW, Sack MJ, Yu GH, Livolsi VA, Gupta PK. Fine-needle aspiration of thyroid: an institutional experience. *Thyroid*. 1998;8:565–9.
11. Oertel YC, Oertel JE. Thyroid cytology and histology. *Baillieres Best Pract Res Clin Endocrinol Metab*. 2000;14:541–57.
12. Centeno BA, Szyfelbein WM, Daniels GH, Vickery AL, Jr. Fine needle aspiration biopsy of the thyroid gland in patients

with prior Graves' disease treated with radioactive iodine. Morphologic findings and potential pitfalls. *Acta Cytol*. 1996; 40:1189–97.
13. Anderson SR, Mandel S, LiVolsi VA, Gupta PK, Baloch ZW. Can cytomorphology differentiate between benign nodules and tumors arising in Graves' disease? *Diagn Cytopathol*. 2004;31: 64–7.
14. Kim WB, Han SM, Kim TY et al. Ultrasonographic screening for detection of thyroid cancer in patients with Graves' disease. *Clin Endocrinol (Oxf)*. 2004;60:719–25.
15. Cantalamessa L, Baldini M, Orsatti A, Meroni L, Amodei V, Castagnone D. Thyroid nodules in Graves disease and the risk of thyroid carcinoma. *Arch Intern Med*. 1999;159:1705–8.
16. MacDonald L, Yazdi HM. Fine needle aspiration biopsy of Hashimoto's thyroiditis. Sources of diagnostic error. *Acta Cytol*. 1999;43:400–6.
17. Mechler C, Bounacer A, Suarez H et al. Papillary thyroid carcinoma: 6 cases from 2 families with associated lymphocytic thyroiditis harbouring RET/PTC rearrangements. *Br J Cancer*. 2001;85:1831–7.
18. Kumar N, Ray C, Jain S. Aspiration cytology of Hashimoto's thyroiditis in an endemic area. *Cytopathology*. 2002;13:31–9.
19. Kumarasinghe MP, De Silva S. Pitfalls in cytological diagnosis of autoimmune thyroiditis. *Pathology*. 1999;31:1–8.
20. Baloch ZW, Fleisher S, LiVolsi VA, Gupta PK. Diagnosis of "follicular neoplasm": A gray zone in thyroid fine-needle aspiration cytology. *Diagn Cytopathol*. 2002;26:41–4.
21. Yang J, Schnadig V, Logrono R, Wasserman PG. Fine-needle aspiration of thyroid nodules: a study of 4703 patients with histologic and clinical correlations. *Cancer*. 2007;111:306–15.
22. Renshaw AA. Follicular lesions of the thyroid. *Am J Clin Pathol*. 2001;115:782–5.
23. Sidawy MK, Del Vecchio DM, Knoll SM. Fine-needle aspiration of thyroid nodules: correlation between cytology and histology and evaluation of discrepant cases. *Cancer*. 1997;81:253–9.
24. Tuttle RM, Lemar H, Burch HB. Clinical features associated with an increased risk of thyroid malignancy in patients with follicular neoplasia by fine-needle aspiration. *Thyroid*. 1998; 8:377–83.
25. Kini SR, Miller JM, Hamburger JI, Smith-Purslow MJ. Cytopathology of follicular lesions of the thyroid gland. *Diagnostic Cytopathology*. 1985;1:123–32.
26. Elliott DD, Pitman MB, Bloom L, Faquin WC. Fine-needle aspiration biopsy of Hurthle cell lesions of the thyroid gland: A cytomorphologic study of 139 cases with statistical analysis. *Cancer*. 2006;108:102–9.
27. Carcangui ML ZG, Pupi A, Castagnoli A, Rosai J. Papillary carcinoma of the thyroid: a clinico-pathologic study of 241 cases treated at the University of Florence, Italy. *Cancer*. 1985;55:805–828.
28. Oertel YC. Fine-Needle Aspiration in the Evaluation of Thyroid Neoplasms. *Endocr Pathol*. 1997;8:215–224.
29. Das DK, Mallik MK, Sharma P et al. Papillary thyroid carcinoma and its variants in fine needle aspiration smears. A cytomorphologic study with special reference to tall cell variant. *Acta Cytol*. 2004;48:325–36.
30. Baloch ZW, LiVolsi VA. Cytologic and architectural mimics of papillary thyroid carcinoma. Diagnostic challenges in fine-needle aspiration and surgical pathology specimens. *Am J Clin Pathol*. 2006;125 Suppl:S135–44.
31. Albores-Saavedra J, Wu J. The many faces and mimics of papillary thyroid carcinoma. *Endocr Pathol*. 2006;17:1–18.
32. Zacks JF, de las Morenas A, Beazley RM, O'Brien MJ. Fine-needle aspiration cytology diagnosis of colloid nodule versus follicular variant of papillary carcinoma of the thyroid. *Diagn Cytopathol*. 1998;18:87–90.
33. Solomon A, Gupta PK, LiVolsi VA, Baloch ZW. Distinguishing tall cell variant of papillary thyroid carcinoma from usual variant of papillary thyroid carcinoma in cytologic specimens. *Diagn Cytopathol*. 2002;27:143–8.
34. Murray D. *The Thyroid Gland*. Malden, MA: Blackwell Science; 1998:295–380.
35. Collins BT, Cramer HM, Tabatowski K, Hearn S, Raminhos A, Lampe H. Fine needle aspiration of medullary carcinoma of the thyroid. Cytomorphology, immunocytochemistry and electron microscopy. *Acta Cytol*. 1995;39:920–30.
36. Papaparaskeva K, Nagel H, Droese M. Cytologic diagnosis of medullary carcinoma of the thyroid gland. *Diagn Cytopathol*. 2000;22:351–8.
37. Saunders CA, Nayar R. Anaplastic spindle-cell squamous carcinoma arising in association with tall-cell papillary cancer of the thyroid: A potential pitfall. *Diagn Cytopathol*. 1999;21:413–8.
38. Bejarano PA, Nikiforov YE, Swenson ES, Biddinger PW. Thyroid transcription factor-1, thyroglobulin, cytokeratin 7, and cytokeratin 20 in thyroid neoplasms. *Appl Immunohistochem Mol Morphol*. 2000;8:189–94.
39. Davila RM, Bedrossian CW, Silverberg AB. Immunocytochemistry of the thyroid in surgical and cytologic specimens. *Arch Pathol Lab Med*. 1988;112:51–6.
40. Cheung CC, Ezzat S, Freeman JL, Rosen IB, Asa SL. Immunohistochemical diagnosis of papillary thyroid carcinoma. *Mod Pathol*. 2001;14:338–42.
41. Sapio MR, Guerra A, Posca D et al. Combined analysis of galectin-3 and BRAFV600E improves the accuracy of fine-needle aspiration biopsy with cytological findings suspicious for papillary thyroid carcinoma. *Endocr Relat Cancer*. 2007;14:1089–97.
42. Barroeta JE, Baloch ZW, Lal P, Pasha TL, Zhang PJ, LiVolsi VA. Diagnostic value of differential expression of CK19, Galectin-3, HBME-1, ERK, RET, and p16 in benign and malignant follicular-derived lesions of the thyroid: an immunohistochemical tissue microarray analysis. *Endocr Pathol*. 2006;17:225–34.
43. Nikiforov YE. RET/PTC Rearrangement in Thyroid Tumors. *Endocr Pathol*. 2002;13:3–16.
44. Fischer AH, Bond JA, Taysavang P, O.Eugene B, Wynford-Thomas D. Papillary thyroid carcinoma oncogene (RET/PTC) alters the nuclear envelope and chromatin structure. *Am J Pathol*. 1998;153:1443–1450.
45. Zou M, Shi Y, Farid NR. Low rate of ret proto-oncogene activation (PTC/retTPC) in papillary thyroid carcinomas from Saudi Arabia. *Cancer*. 1994;73:176–80.
46. Motomura T, Nikiforov YE, Namba H et al. ret rearrangements in Japanese pediatric and adult papillary thyroid cancers. *Thyroid*. 1998;8:485–9.
47. Sapio MR, Posca D, Raggioli A et al. Detection of RET/PTC, TRK and BRAF mutations in preoperative diagnosis of thyroid nodules with indeterminate cytological findings. *Clin Endocrinol (Oxf)*. 2007;66:678–83.
48. Pizzolanti G, Russo L, Richiusa P et al. Fine-needle aspiration molecular analysis for the diagnosis of papillary thyroid carcinoma through BRAF V600E mutation and RET/PTC rearrangement. *Thyroid*. 2007;17:1109–15.
49. Papotti M, Volante M, Giuliano A et al. RET/PTC activation in hyalinizing trabecular tumors of the thyroid. *Am J Surg Pathol*. 2000;24:1615–21.
50. Wirtschafter A, Schmidt R, Rosen D et al. Expression of the RET/PTC fusion gene as a marker for papillary carcinoma in Hashimoto's thyroiditis. [see comments]. *Laryngoscope*. 1997;107:95–100.
51. Elisei R, Romei C, Vorontsova T et al. RET/PTC rearrangements in thyroid nodules: studies in irradiated and not irradiated, malignant and benign thyroid lesions in children and adults. *J Clin Endocrinol Metab*. 2001;86:3211–6.

52. Inaba M, Umemura S, Satoh H et al. Expression of RET in follicular cell-derived tumors of the thyroid gland: Prevalence and implication of morphological type. *Pathol Int*. 2003;53:146–53.
53. Cohen Y, Xing M, Mambo E et al. BRAF mutation in papillary thyroid carcinoma. *J Natl Cancer Inst*. 2003;95:625–7.
54. Kimura ET, Nikiforova MN, Zhu Z, Knauf JA, Nikiforov YE, Fagin JA. High prevalence of BRAF mutations in thyroid cancer: genetic evidence for constitutive activation of the RET/PTC-RAS-BRAF signaling pathway in papillary thyroid carcinoma. *Cancer Res*. 2003;63:1454–7.
55. Fagin JA. How thyroid tumors start and why it matters: kinase mutants as targets for solid cancer pharmacotherapy. *J Endocrinol*. 2004;183:249–56.
56. Lubitz CC, Ugras SK, Kazam JJ et al. Microarray analysis of thyroid nodule fine-needle aspirates accurately classifies benign and malignant lesions. *J Mol Diagn*. 2006;8:490–8; quiz 528.
57. Liu F, Gnepp DR, Pisharodi LR. Fine needle aspiration of parathyroid lesions. *Acta Cytol*. 2004;48:133–6.
58. Maser C, Donovan P, Santos F et al. Sonographically guided fine needle aspiration with rapid parathyroid hormone assay. *Ann Surg Oncol*. 2006;13:1690–5.
59. Tseleni-Balafouta S, Gakiopoulou H, Kavantzas N, Agrogiannis G, Givalos N, Patsouris E. Parathyroid proliferations: a source of diagnostic pitfalls in FNA of thyroid. *Cancer*. 2007;111:130–6.
60. Owens CL, Rekhtman N, Sokoll L, Ali SZ. Parathyroid hormone assay in fine-needle aspirate is useful in differentiating inadvertently sampled parathyroid tissue from thyroid lesions. *Diagn Cytopathol*. 2008;36:227–31.
61. Giorgadze T, Stratton B, Baloch ZW, Livolsi VA. Oncocytic parathyroid adenoma: problem in cytological diagnosis. *Diagn Cytopathol*. 2004;31:276–80.
62. Abati A, Skarulis MC, Shawker T, Solomon D. Ultrasound-guided fine-needle aspiration of parathyroid lesions: a morphological and immunocytochemical approach. *Hum Pathol*. 1995;26:338–43.
63. Lumachi F, Borsato S, Brandes AA et al. Fine-needle aspiration cytology of adrenal masses in noncancer patients: clinicoradiologic and histologic correlations in functioning and nonfunctioning tumors. *Cancer*. 2001;93:323–9.
64. Lumachi F, Basso SM, Borsato S et al. Role and cost-effectiveness of adrenal imaging and image-guided FNA cytology in the management of incidentally discovered adrenal tumours. *Anticancer Res*. 2005;25:4559–62.
65. Fassina AS, Borsato S, Fedeli U. Fine needle aspiration cytology (FNAC) of adrenal masses. *Cytopathology*. 2000; 11:302–11.
66. Wu HH, Cramer HM, Kho J, Elsheikh TM. Fine needle aspiration cytology of benign adrenal cortical nodules. A comparison of cytologic findings with those of primary and metastatic adrenal malignancies. *Acta Cytol*. 1998;42:1352–8.
67. Sharma S, Singh R, Verma K. Cytomorphology of adrenocortical carcinoma and comparison with renal cell carcinoma. *Acta Cytol*. 1997;41:385–92.
68. Cochand-Priollet B. [Cytology of renal and adrenal gland masses in adults]. *Arch Anat Cytol Pathol*. 1997;45:299–304.
69. DeWitt J, Alsatie M, LeBlanc J, McHenry L, Sherman S. Endoscopic ultrasound-guided fine-needle aspiration of left adrenal gland masses. *Endoscopy*. 2007;39:65–71.
70. Jhala NC, Jhala D, Eloubeidi MA et al. Endoscopic ultrasound-guided fine-needle aspiration biopsy of the adrenal glands: analysis of 24 patients. *Cancer*. 2004;102:308–14.
71. Eloubeidi MA, Tamhane A, Jhala N et al. Agreement between rapid onsite and final cytologic interpretations of EUS-guided FNA specimens: implications for the endosonographer and patient management. *Am J Gastroenterol*. 2006;101:2841–7.
72. Jimenez-Heffernan JA, Vicandi B, Lopez-Ferrer P, Gonzalez-Peramato P, Perez-Campos A, Viguer JM. Cytologic features of pheochromocytoma and retroperitoneal paraganglioma: a morphologic and immunohistochemical study of 13 cases. *Acta Cytol*. 2006;50:372–8.
73. Saboorian MH, Katz RL, Charnsangavej C. Fine needle aspiration cytology of primary and metastatic lesions of the adrenal gland. A series of 188 biopsies with radiologic correlation. *Acta Cytol*. 1995;39:843–51.
74. Chatzipantelis P, Salla C, Konstantinou P, Karoumpalis I, Sakellariou S, Doumani I. Endoscopic ultrasound-guided fine-needle aspiration cytology of pancreatic neuroendocrine tumors: a study of 48 cases. *Cancer*. 2008.
75. Chang F, Vu C, Chandra A, Meenan J, Herbert A. Endoscopic ultrasound-guided fine needle aspiration cytology of pancreatic neuroendocrine tumours: cytomorphological and immunocytochemical evaluation. *Cytopathology*. 2006;17:10–7.
76. Gu M, Ghafari S, Lin F, Ramzy I. Cytological diagnosis of endocrine tumors of the pancreas by endoscopic ultrasound-guided fine-needle aspiration biopsy. *Diagn Cytopathol*. 2005; 32:204–10.
77. Jimenez-Heffernan JA, Vicandi B, Lopez-Ferrer P, Gonzalez-Peramato P, Perez-Campos A, Viguer JM. Fine needle aspiration cytology of endocrine neoplasms of the pancreas. Morphologic and immunocytochemical findings in 20 cases. *Acta Cytol*. 2004;48:295–301.
78. Saez A, Catala I, Brossa R, Funes A, Jaurrieta E, Ferrer JE. Intraoperative fine needle aspiration cytology of pancreatic lesions. A study of 90 cases. *Acta Cytol*. 1995;39:485–8.
79. Deshpande V, Lauwers GY. Cystic pancreatic endocrine tumor: a variant commonly confused with cystic adenocarcinoma. *Cancer*. 2007;111:47–53.
80. Pacchioni D, Papotti M, Macri L, Forte G, Bussolati G. Pancreatic oncocytic endocrine tumors. Cytologic features of two cases. *Acta Cytol*. 1996;40:742–6.
81. Guarda LA, Silva EG, Ordonez NG, Mackay B, Ibanez ML. Clear cell islet cell tumor. *Am J Clin Pathol*. 1983;79:512–7.
82. Hoang MP, Hruban RH, Albores-Saavedra J. Clear cell endocrine pancreatic tumor mimicking renal cell carcinoma: a distinctive neoplasm of von Hippel-Lindau disease. *Am J Surg Pathol*. 2001;25:602–9.
83. Shaw JA, Vance RP, Geisinger KR, Marshall RB. Islet cell neoplasms. A fine-needle aspiration cytology study with immunocytochemical correlations. *Am J Clin Pathol*. 1990;94:142–9.
84. Skacel M, Ormsby AH, Petras RE, McMahon JT, Henricks WH. Immunohistochemistry in the differential diagnosis of acinar and endocrine pancreatic neoplasms. *Appl Immunohistochem Mol Morphol*. 2000;8:203–9.
85. Labate AM, Klimstra DL, Zakowski MF. Comparative cytologic features of pancreatic acinar cell carcinoma and islet cell tumor. *Diagn Cytopathol*. 1997;16:112–6.

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