Distinguishing Parathyroid and Thyroid Lesions on Ultrasound-Guided Fine-Needle Aspiration: A Correlation of Clinical Data, Ancillary Studies, and Molecular Analysis

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BACKGROUND: Differentiating parathyroid and thyroid lesions can be challenging because of considerable morphologic overlap and anatomic proximity. Therefore, the authors sought to identify characteristic morphologic patterns and useful adjunct tests to distinguish these 2 entities. **METHODS:** A search was conducted in the study institution database for clinically indeterminate thyroid nodules from 2000 through 2016 with an emphasis on confirmed parathyroid nodules. Pathology reports, slides, ancillary studies, molecular analysis, and clinical and radiologic data were retrieved. **RESULTS:** A total of 143 cases of clinically indeterminate thyroid nodules were identified; 34 of these were confirmed parathyroid nodules. Three cytologic patterns were identified: 1) oncocytic cell pattern (9 cases; 26%); 2) follicular lesion of undetermined significance-like/papillary-like pattern (14 cases; 41%); and 3) nonspecific endocrine cell clusters (11 cases; 32%). Bare oval nuclei (100%), nuclear overlap (88%), crowded sheets (88%), and intracytoplasmic vacuoles (62%) were observed. Ten cases (29%) demonstrated positive immunostaining for parathyroid hormone (PTH), 7 cases (21%) demonstrated a positive PTH assay, and 9 cases (26%) had PTH detected by ThyroSeq v.2. The remaining 8 cases were morphologically either indeterminate or suggestive of parathyroid origin. The cytologic diagnosis was confirmed clinically (20 cases) or surgically (14 cases). Based on cytology alone, 8 cases initially were diagnosed as thyroid tissue and amended to parathyroid lesion after ancillary studies were performed, including 5 cases based on ThyroSeq v.2 results alone. **CONCLUSIONS:** Lesions with follicular lesion of undetermined significance-like or oncocytic features are prone to misdiagnosis. The current study identified distinct cytologic patterns in parathyroid lesions suggestive of parathyroid origin, which, together with PTH immunostains or assay, molecular studies, or sestamibi scans, aid in distinguishing parathyroid from thyroid lesions. ***Cancer (Cancer Cytopathol)* 2017;000:000-000**. © *2017 American Cancer Society*.

KEY WORDS: cytomorphology; fine-needle aspiration (FNA); molecular; parathyroid; parathyroid hormone (PTH); thyroid nodule; ThyroSeq.

INTRODUCTION

Fine-needle aspiration (FNA) biopsies have been recognized as a minimally invasive and cost-effective initial assessment of thyroid lesions.[1,2] FNAs aid in patient management, and may eliminate the need for unnecessary surgery.[2] Thyroid aspirates have become common in patients presenting with suspected thyroid masses and have, in turn, led to an increased possibility of aspirating incidental parathyroid lesions. Unsuspected parathyroid tissue, presenting as thyroid lesions, has a reported prevalence of up to 0.4%.[3] Differentiation between parathyroid and thyroid lesions can be challenging because of considerable morphologic overlap as well as close anatomic

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proximity. The recognition of this potential diagnostic pitfall is important to prevent misdiagnosis with subsequent misguided treatment.

Although a combination of clinical, radiologic, and molecular data increase the diagnostic accuracy of parathyroid lesions, familiarity with their cytomorphology will enhance proper diagnostic triage. Despite imaging and localization modalities (ie, sestamibi scan), a few cases may present with atypical locations such as intrathyroidal lesions. Distinguishing thyroid from parathyroid lesions in these cases may not be possible sonographically, and cytopathologists should be aware of the cytomorphologic features of parathyroid aspirates.

To the best of our knowledge, few morphologic studies distinguishing parathyroid from thyroid aspirates have been reported in the literature to date. One study included 12 parathyroid lesions that were compared with thyroid FNA specimens. Seven parathyroid aspirates consisted of moderately cellular smears with cytologic features of cohesive 3-dimensional groups; papillary fragments; microfollicles; cytoplasmic granulation; and background findings of colloid-like material, macrophages, and lymphocytes, which are overlapping features that may be observed in thyroid FNA specimens.[2] Nuclear overlapping and nuclear molding, which are uncommon findings in benign thyroid aspirates, also were reported as findings in parathyroid aspirates.[2] One case series also found similar features.[4] Dimashkieh and Krishnamurthy reported that nuclei measuring smaller than thyroid follicular cells, bare nuclei, stippled chromatin, and a prominent vascular network with adherent cells indicated parathyroid origin.[5] Another study found vascular proliferation, bare nuclei, intracytoplasmic fat vacuolation, and high cellularity to be significantly associated with parathyroid origin.[6]

Histopathology in conjunction with parathyroid hormone (PTH) immunostaining remains the gold standard for accurate diagnosis.[3] Some studies have used immunohistochemical stains on specimens obtained from FNA to differentiate thyroid from parathyroid lesions.[2,7] A high PTH concentration in FNA specimens also has been used to support a parathyroid origin.[8] Furthermore, to the best of our knowledge, only one other study to date has used molecular methods (ie, the Afirma gene expression classifier [GEC]) to confirm indeterminate lesions as being of parathyroid origin.[9]

Cytomorphologic patterns in parathyroid lesions are diverse. The objective of the current study was to examine the cytomorphologic patterns noted in the patient database from the study institution and correlate these patterns with clinical and radiologic data as well as the novel molecular test ThyroSeq v.2 to further clarify this challenging area of cytopathology. To our knowledge, the current study is the first to date to compare parathyroid with thyroid tissue on cytology in cytomorphology, radiology, and ThyroSeq v.2 molecular profiles.

MATERIALS AND METHODS

The protocol was approved by the New York University Institutional Review Board. The institution's pathology database was searched for indeterminate cases of thyroid FNA specimens (thyroid vs parathyroid) from 2000 through 2016, with a focus on cases confirmed to be parathyroid. Pathology reports, smears, and cell blocks from FNAs were retrieved from the diagnostic archives of the pathology department. Pathology diagnoses were recorded and slides were reviewed retrospectively. Clinical data including PTH, calcium serum levels, and imaging studies (ie, ultrasound or sestamibi) reports were retrieved and recorded from the patient medical records. Results of molecular studies including ThyroSeq v.2 also were recorded.

FNA Specimen Collection

Ultrasound-guided thyroid FNA was performed by cytopathologists and, in a subset of cases, in conjunction with a radiologist. An average of 2 to 4 passes were performed using 25-gauge to 27-gauge needles. Air-dried smears were prepared with Diff-Quik and rapid Papanicolaou stains. A subset of cases had immunohistochemical stains performed on the cell block and/or on unstained air-dried smears. When sent for PTH assay (Mayo Medical Laboratories, Rochester, Minnesota), FNA needle wash samples were collected in saline with a total fluid volume of 1 to 1.5 mL.

RESULTS

A total of 143 cases were retrieved; of these, 34 cases (24%) ultimately were confirmed to be parathyroid tissue either clinically or surgically. Three cytologic patterns were identified among the 34 parathyroid tissue cases (Tables 1 and 2): 1) an oncocytic cell pattern in 9 cases (26%); 2) a follicular lesion of undetermined significance (FLUS)-like/papillary-like pattern in 14 cases (41%); and 3) nonspecific endocrine cell clusters in 11 cases (32%) (Table 1) (Fig. 1).

TABLE 1. Morphologic Patterns in Parathyroid Aspirates

Morphology	No. (%) N = 34
Oncocytic cell pattern	9 (26%)
FLUS-like/papillary-like pattern	14 (41%)
Nonspecific endocrine cell pattern	11 (32%)

Abbreviation: FLUS, follicular lesion of undetermined significance.

TABLE 2. Morphologic Features in Parathyroid Aspirates

Morphology	No. (%) N = 34
Bare nuclei	34 (100%)
Nuclear overlap	30 (88%)
Crowded sheets	30 (88%)
Papillary-like structures	12 (35%)
Cytoplasmic vacuoles	21 (62%)
Colloid-like material	18 (53%)

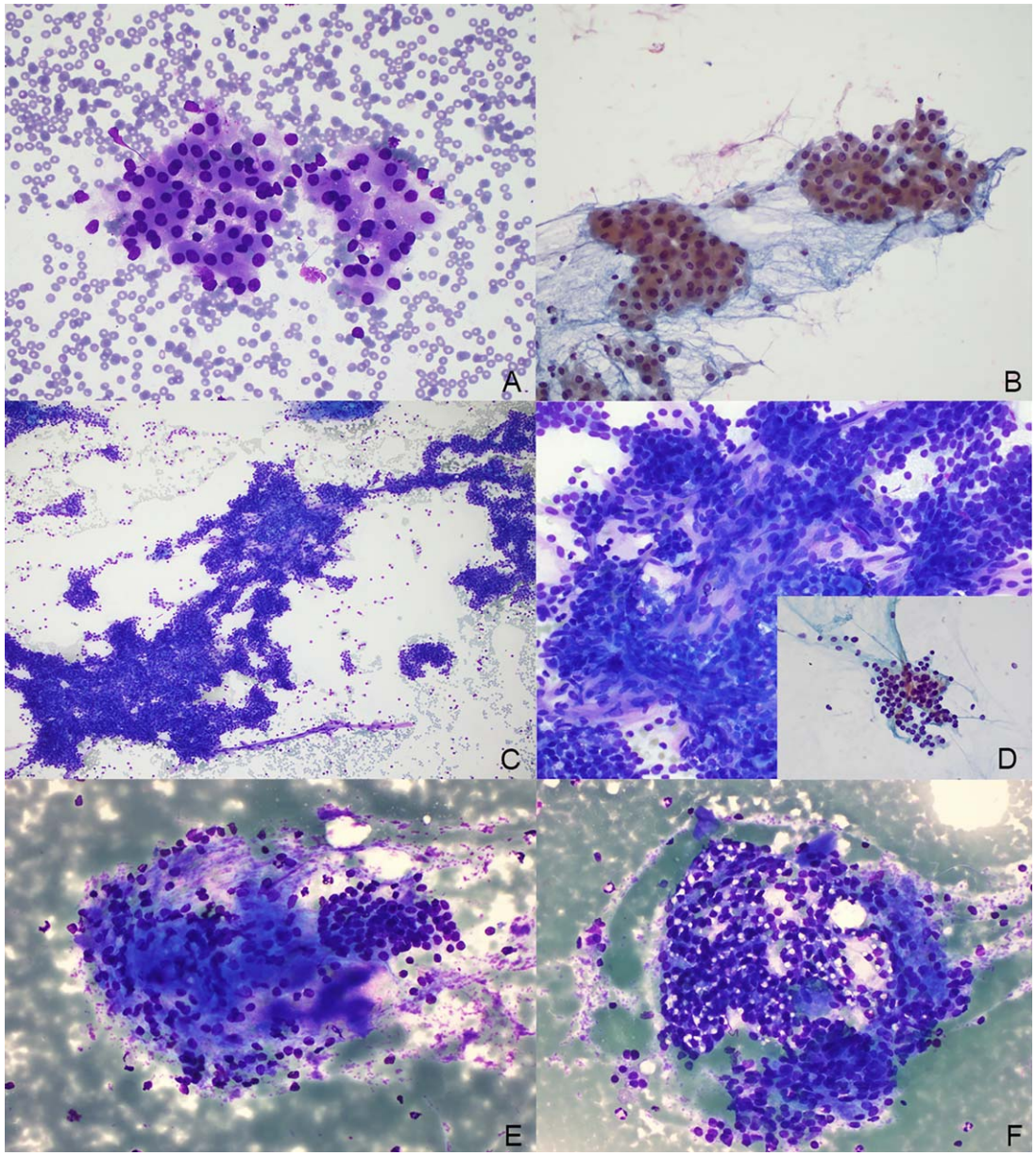

Figure 1. (A) Oncocytic cell pattern (Diff-Quik stain, original magnification ×400). (B) Oncocytic cell pattern (rapid Papanicolaou stain, original magnification ×400). (C) Follicular lesion of undetermined significance (FLUS)-like/papillary-like pattern (Diff-Quik stain, original magnification ×100). (D) FLUS-like/papillary-like pattern with delicate vessels (Diff-Quik stain, original magnification ×400). *Inset*: Round nuclei lacking cytologic atypia (rapid Papanicolaou stain, original magnification ×600). (E) Nonspecific endocrine cell clusters with colloid-like material (Diff-Quik stain, original magnification ×400). (F) Intracytoplasmic vacuoles (Diff-Quik stain, original magnification ×400).

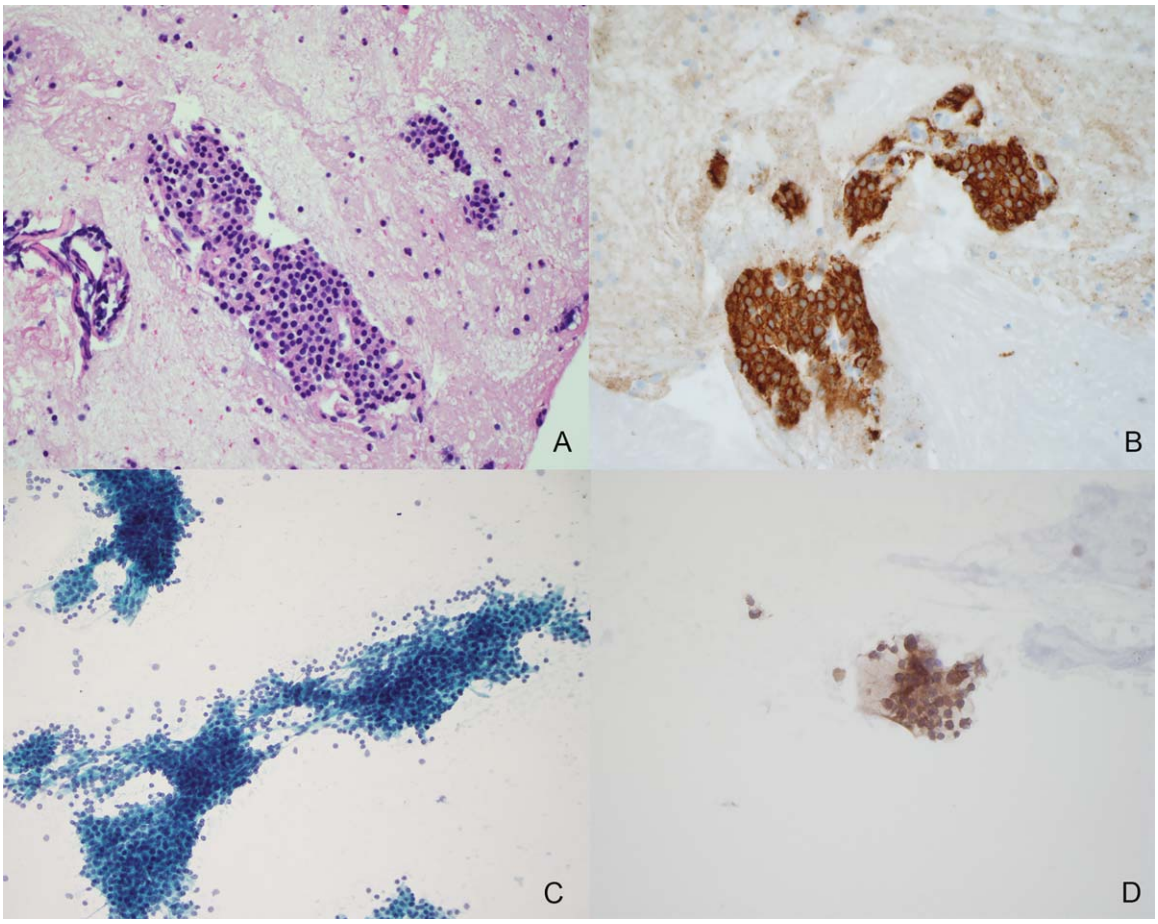

Figure 2. (A) Parathyroid tissue on cell block (H & E, original magnification ×400). (B) Parathyroid hormone immunostaining (original magnification ×400). (C) Parathyroid aspirate (rapid Papanicolaou stain, original magnification ×200). (D) GATA-binding protein 3 (GATA-3) immunostaining (original magnification ×400).

The oncocytic cell pattern included hypercellular smears that were composed almost exclusively of oncocytic cells. The FLUS-like/papillary-like pattern included hypercellular smears associated with prominent vascular networks and occasional microfollicles. Cytologic atypia was not noted. The nonspecific endocrine cell pattern included predominantly hypocellular to moderately cellular smears arranged in nonspecific endocrine cell clusters.

Among the 34 cases and across all 3 cytologic patterns, consistent features included bare oval nuclei (100%), nuclear overlap (88%), crowded sheets (88%), and cytoplasmic vacuoles (62%) (Fig. 1F). The nuclei were round with dark chromatin, and stippled chromatin was not prominent (Fig. 1D inset). Papillary-like structures with prominent vascular proliferation were observed in 12 cases (35%). The confounding feature of colloid-like material was noted in 18 cases (53%) (Fig. 1E).

TABLE 3. Confirmatory Ancillary Tests in Parathyroid Aspirates

Confirmatory Ancillary Test	No. (%)
PTH immunostaining (performed on cell block or direct smears)	10 (29%)
PTH assay	7 (21%)
ThyroSeq v.2 molecular test	9 (26%)

Abbreviation: PTH, parathyroid hormone.

On cytology, 26 cases (76%) were confirmed to be parathyroid with the support of ancillary studies. Ten cases (29%) demonstrated positive immunostaining for PTH and 1 case also was positive for GATA-binding protein 3 (GATA-3) (Fig. 2); 7 cases (21%) were positive for PTH assay, and 9 cases (26%) had PTH genes detected by ThyroSeq v.2 (Table 3). Thyroid transcription factor 1 (TTF-1) and thyroglobulin immunostains, when performed, were negative.

TABLE 4. Eight Cases Amended From Thyroid Tissue to Parathyroid Lesion

Prior Diagnosis	Pattern	Confirmed By
Benign (Bethesda class II) (3 cases)	Nonspecific endocrine cell (3 cases)	PTH immunostaining/PTH assay (3 cases)
FLUS (Bethesda class III) (3 cases)	Oncocytic cell (1 case), FLUS-like (1 case), and nonspecific endocrine cell (1 case)	ThyroSeq v.2 (3 cases)
Follicular neoplasm (Bethesda class IV) (2 cases)	Oncocytic cell (1 case) and FLUS-like (1 case)	ThyroSeq v.2 (2 cases)

Abbreviations: FLUS, follicular lesion of undetermined significance; PTH, parathyroid hormone.

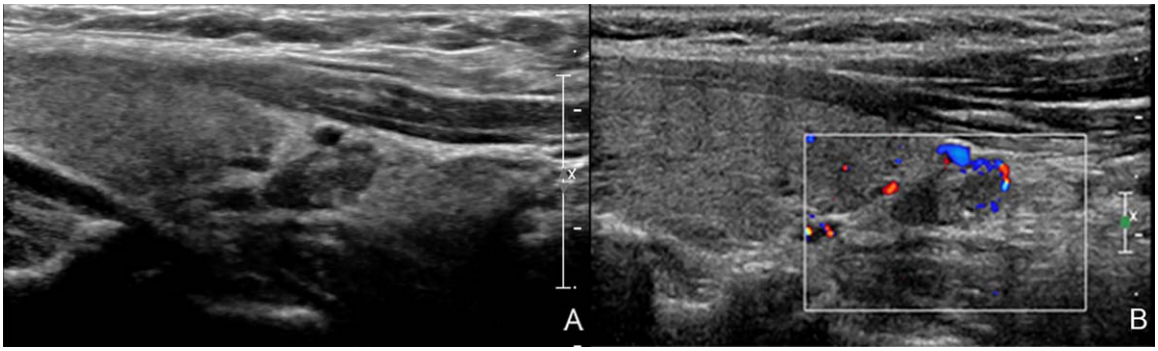

Figure 3. (A) Ultrasound demonstrating typical features (ovoid, hypoechoic) of parathyroid adenoma with (B) peripheral vascularity observed on color Doppler imaging.

In the remaining 8 cases (24%), the diagnosis, based on cytomorphology alone, was either indeterminate or only suggestive of parathyroid origin. These cases were confirmed to be parathyroid with the support of sestamibi scans, a clinical presentation of hyperparathyroidism, hypercalcemia, and/or surgical excision.

The cytologic diagnosis of the 34 cases was confirmed clinically in 20 cases (59%) with medical management and surgically in 14 cases (41%). The histologic diagnoses of surgically excised cases included hypercellular parathyroid tissue and parathyroid adenoma. Based on cytology alone, 8 cases (24%) initially were incorrectly diagnosed as thyroid tissue and amended to parathyroid lesion after ancillary studies were performed, including 5 cases based on ThyroSeq v.2 results alone (Table 4).

Radiologically, the parathyroid lesions ranged from 0.5 cm to 3.4 cm in largest dimension. In terms of sonographic findings, only 7 cases (21%) were found to have typical features of a parathyroid adenoma on ultrasound (Fig. 3). Typical features included hypoechoic, oval, solid nodules with peripheral and internal vascularity. Ultrasound characteristics of the other parathyroid lesions were variable and ranged from avascular complex solid/cystic to echogenic in architecture. Twelve cases (35%) were intrathyroidal in location. Additional ipsilateral thyroid nodules were observed in 13 cases (38%).

Sestamibi scans were supportive of parathyroid lesions in 10 cases. Three cases had sestamibi scans that were negative for any evidence of parathyroid lesions despite the findings of hyperparathyroidism and subsequent confirmation of parathyroid tissue by ancillary studies and/or surgical excision. Sestamibi scan results were either unavailable or the scan was not performed in the remaining cases.

Of 34 cases, 23 presented clinically with hyperparathyroidism (intact PTH serum levels >15-75 pg/mL) and hypercalcemia (serum calcium levels >8.3-10.3 mg/dL). The remaining cases ultimately were confirmed to be parathyroid lesions based on cytopathology workup with ancillary PTH immunostaining/assay or ThyroSeq v.2.

DISCUSSION

Ultrasound imaging and technetium sestamibi scintigraphy are the main techniques for the preoperative localization of parathyroid adenomas.[10] Typical features of parathyroid adenomas include hypoechoic, oval, or bean-shaped lesions, with color Doppler imaging commonly demonstrating a characteristic extrathyroidal feeding vessel and internal vascularity noted in a peripheral distribution.[10] Studies have shown that parathyroid adenomas with a feeding vessel were correctly identified in 73% to 93% of

cases, and for suspected adenomas without a feeding vessel, localization was correct only 39% of the time.[11,12] The combined use of ultrasound with sestamibi scintigraphy has a sensitivity of 95% versus 80% for sonography alone and 87% for scintigraphy alone.[13]

However, these imaging modalities have their limitations. Imaging pitfalls may be observed, especially when there is concomitant thyroid disease.[10] Multinodular thyroid glands may present with posterior nodules that mimic parathyroid lesions, and intrathyroid parathyroid glands may be difficult to distinguish from a thyroid nodule.[10] In the current study, approximately 35% of cases were intrathyroidal in location, and additional ipsilateral thyroid nodules were observed in 38% of cases. Furthermore, only 21% of the cases in the current study were found to have typical features of a parathyroid adenoma on ultrasound. Of 13 cases evaluated with a sestamibi scan, 3 were negative for any evidence of parathyroid lesions despite the findings of hyperparathyroidism, subsequent confirmation of parathyroid tissue by ancillary studies, and/or surgical excision. Although sestamibi scans have been reported to have correctly detected and localized 19 of 21 adenomas (90%),[14] more recent studies have reported false-negative results in approximately 25% of adenomas.[15,16] Significant factors that predict accurate detection include gland size and volume, and it has been postulated that enlarging glands become more active metabolically and are more easily detected on sestamibi scan.[17] In the current study, the parathyroid lesions ranged from 0.5 cm to 3.4 cm in largest dimension. Two cases that were negative on sestamibi scan were subcentimeter in size.

Of 34 cases, 23 clinically presented with hyperparathyroidism (intact PTH serum levels >15-75 pg/mL) and hypercalcemia (serum calcium levels >8.3-10.3 mg/dL). The remaining cases ultimately were confirmed to be parathyroid lesions based on cytopathology workup with ancillary PTH immunostaining/assay or ThyroSeq v.2. Thus, we emphasize the need for a combined approach with cytomorphology and ancillary studies, especially in incidental parathyroid lesions without a clinical suspicion of hyperparathyroidism.

Common major cytomorphologic features of parathyroid tissue that have been reported in the literature include a papillary-like pattern with fibrovascular cores or prominent vascular network/proliferation, stippled chromatin, follicular pattern, and bare nuclei (Table 5).[2,4–9,18–22] The majority of these studies also concluded that a combination of cytomorphologic features supported by either ancillary studies or correlation with clinical, radiologic, and laboratory findings are important in establishing a correct diagnosis of parathyroid tissue. The main diagnostic features in the current study also included bare nuclei. A papillary-like pattern was observed in only a subset of cases reported herein. The other main diagnostic features noted in the current study were crowded clusters with a lack of polarity and intracytoplasmic fat vacuoles.

Ancillary studies including the PTH assay and PTH immunostains were used in the current study to support parathyroid origin. The usefulness of detecting PTH in the aspirate has been well established in the literature, with a strong positive correlation observed between high levels (>245 pg/mL) of PTH in the FNA specimen and the histological findings of parathyroid lesions.[23] The parathyroid aspirates in the current study ranged from 95 pg/mL to 14,844 pg/mL. The PTH assay requires the prompt handling of fresh samples. Therefore, immediate assessment of the FNA specimen is necessary to obtain and process such a sample, particularly when the diagnosis has not been considered clinically. The usefulness of the PTH immunohistochemical stain on specimens obtained from FNA to differentiate thyroid from parathyroid lesions has been previously reported.[2,7] Recently, GATA-3 has been shown to be a useful immunohistochemical stain in differentiating parathyroid from thyroid lesions. In one study, liquid-based cytologic preparations of 35 parathyroid lesions demonstrated 97.1% of cases to have positive immunostaining for GATA-3 and PTH. Conventional smears in the same study demonstrated that all parathyroid-derived cells and even naked nuclei were strongly positive for GATA-3, whereas positive PTH staining was noted in only 25.5% of cases ($P<.01$).[24] In discriminating parathyroid from thyroid lesions on surgical specimens, GATA-3 has been shown to have a sensitivity of 100% and a specificity of 97%.[25] In the current study, GATA-3 immunohistochemistry was performed in only 1 case and was positive in the parathyroid aspirate in conjunction with PTH immunopositivity.

To the best of our knowledge, little has been reported regarding the usefulness of molecular methods in the detection of parathyroid lesions. One study used the Afirma GEC to confirm indeterminate lesions as being of parathyroid origin. Thirteen samples that were indeterminate thyroid nodules subsequently were detected by the GEC to have a parathyroid gene expression signature.[9] The cases in

TABLE 5. Mini Literature Review of Parathyroid Cytomorphology

Study	No. of Parathyroid Cases	No. of Cases Misdiagnosed as Thyroid Tissue	Cytomorphology[a]	Confirmatory Ancillary Studies
Abati 1995[7]	12	0	• **Cellular fragments** • Microacini • Trabecular architecture • **Vascular proliferation**	PTH radioimmunoassay; immunostain
Absher 2002[2]	12	0	• Cellular fragments • Papillary fragments • Microfollicles • Bare nuclei • **Nuclear overlapping** • Nuclear molding	PTH assay; immunostain
Tseng 2002[8]	72	6	• **Cellular fragments** • Follicular structures • Colloid-like substance • Nuclear pleomorphism	Histologic confirmation; PTH assay
Giorgadze 2004[22]	2	2	• **Cellular fragments** • Microfollicles • **Oncocytic cells** • Vascular proliferation • Bare nuclei	Histologic confirmation
Liu 2004[21]	14	0	• Cellular fragments • Microfollicles • **Bare nuclei** • Nuclear pleomorphism	Histologic/intraoperative confirmation
Dimashkieh & Krishnamurthy 2006[5]	20	0	• Cellular fragments • **Stippled chromatin** • Bare nuclei • **Vascular proliferation**	Immunostain
Paker 2010[20]	1	1	• Cellular fragments • Oncocytic cells • Vascular proliferation	Histologic confirmation
Papanicolau-Sengos 2013[19]	1	1	• Cellular fragments • Microfollicles • Granular cytoplasm	Histologic confirmation
Agarwal & Kaushal 2016[4]	3	0	• **Cellular fragments** • Follicular pattern • Round nucleus • Stippled chromatin • Nuclear overlapping • **Vascular proliferation**	Histologic confirmation
Kumari 2016[6]	15	0	• Cellular fragments • **Vascular proliferation** • Bare nuclei • **Intracytoplasmic vacuolation** • Absence of colloid	Histologic confirmation
Shi 2016[18]	2	1	• Cellular fragments • Bare nuclei • Stippled chromatin • Oncocytic cells • **Vascular proliferation**	Histologic confirmation
Domingo 2017[9]	60	13	• **Cellular fragments** • Small, dark nuclei • Oncocytic changes • Bare nuclei	Immunostain; Afirma GEC
Current study	34	8	• Crowded sheets • Nuclear overlap • Papillary-like structures • **Bare nuclei** • Cytoplasmic vacuoles • Colloid-like material	Immunostain; PTH assay; ThyroSeq v.2

Abbreviations: GEC, gene expression classifier; PTH, parathyroid hormone.
[a] Predominant features are shown in bold type.

the current study underwent molecular testing using the ThyroSeq v.2 next-generation sequencing assay because it is the preferred molecular test of the study institution. The ThyroSeq v.2 panel included 14 genes analyzed for point mutations, 42 types of gene fusions occurring in thyroid cancer, and 8 genes assessed for expression to evaluate the cell composition of FNA samples including the PTH gene.[26] In the current study, ThyroSeq v.2 detected the PTH gene in 9 cases. Based on cytology alone, 8 cases (24%) initially were diagnosed incorrectly as thyroid tissue and amended to a diagnosis of parathyroid lesion, including 5 cases based on ThyroSeq v.2 results alone. In these incidental unsuspected cases, molecular studies proved to be valuable. It is interesting to note that in 1 case, a concomitant phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) mutation (p.H1047R, c.3140A>G) was detected. The diagnostic significance of this mutation is unknown. To our knowledge, one case of a sporadic parathyroid carcinoma carrying the *PIK3CA* mutation has been reported to date.[27] The patient in the current study with this mutation did not undergo surgical excision. Otherwise, no cases of parathyroid carcinoma were noted in the current study. Given that many aspirates (68% in the current study) may be mistaken cytologically for atypical thyroid lesions (oncocytic or FLUS-like/papillary-like), molecular testing is particularly valuable. ThyroSeq v.2 primarily assesses for the presence of thyroid cancer-associated genes and mutations when the tissue is of thyroid origin, but has the added benefit of detecting parathyroid genes. This provides useful management information regardless of whether the lesion is of thyroid or parathyroid origin.

Conclusions

The current study describes the cytomorphologic features of parathyroid lesions as well as the important ancillary tests that should be used to achieve the proper diagnosis of a parathyroid lesion in cases that clinically and sonographically appear to be thyroidal lesions. Cytomorphologically, 3 cytologic patterns were identified: 1) a oncocytic cell pattern; 2) a FLUS-like/papillary-like pattern; and 3) nonspecific endocrine cell clusters. In addition, the main diagnostic features elucidated in the current study were crowded clusters with a lack of polarity, intracytoplasmic vacuoles, and bare nuclei. Cytologic pitfalls leading to misdiagnosis included abundant thick colloid and the presence of an oncocytic cell pattern. In these settings, helpful adjuncts to the diagnosis include PTH immunostains/assay, sestamibi scan, and molecular studies. The key is maintaining awareness of these morphologic patterns, which can aid with triage toward further parathyroid diagnostic testing.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Margaret Cho: Conceptualization, methodology, investigation, data curation, project administration, writing-original draft, writing-review and editing, and visualization. **Thaira Oweity**: Conceptualization, investigation, methodology, writing-review and editing, supervision, project administration, and visualization. **Tamar C. Brandler**: Methodology, investigation, and writing-review and editing. **Karen Fried**: Writing-review and editing. **Pascale Levine**: Conceptualization, investigation, methodology, data curation, writing-review and editing, supervision, project administration, and visualization.

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