Thyroid Paraganglioma: A Diagnostic Pitfall in Thyroid FNA

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BACKGROUND: Thyroid paragangliomas are extremely rare and often are misdiagnosed by preoperative fine-needle aspiration (FNA) because their cytologic features overlap with those of other thyroid neoplasms. The objective of this study was to review the cytomorphology in a series of thyroid paragangliomas and correlate the findings with histopathology. **METHODS:** Five thyroid paraganglioma cases that underwent FNA were reviewed. Their clinical presentation, radiology features, cytomorphology, ancillary tests, and histopathology were analyzed. **RESULTS:** All patients were women with an average age of 49 years (age range, 35-61 years) and presented with an asymptomatic, solitary thyroid nodule. Radiologically, these nodules (size range, 1.8-3.0 cm) were well circumscribed, hypoechoic, and hypervascular. FNA smears showed clusters of loosely cohesive, medium-to-large epithelioid cells with clear-to-eosinophilic and occasionally foamy cytoplasm that had indistinct cytoplasmic borders. The nuclei were round to oval with focal nuclear membrane irregularities, inconspicuous nucleoli, focal marked anisonucleosis, and occasional intranuclear pseudoinclusions. Naked nuclei, variable numbers of plasmacytoid cells, multinucleated giant cells, and sustentacular cells were present in the background along with blood vessels and lymphocytes. Cytology diagnoses were incorrect and included follicular neoplasm (n = 4) and follicular lesion of undetermined significance (n = 1). Final histopathology with immunohistochemistry revealed conventional paraganglioma (n = 3) or sclerosing paraganglioma with invasive features (n = 2). **CONCLUSIONS:** All thyroid paragangliomas were misdiagnosed on FNA as follicular neoplasms, in part because of the rarity of these tumors in this location and cytomorphology mimicking follicles. The absence of colloid, the presence of naked nuclei, focal marked anisonucleosis, and the presence of sustentacular cells are important cytology clues. ***Cancer Cytopathol* 2021;129:439-449**. © *2020 American Cancer Society*.

KEY WORDS: cytomorphology; cytopathology; fine-needle aspiration (FNA); paraganglioma; sclerosing paraganglioma; thyroid.

INTRODUCTION

Paragangliomas are slow-growing neuroendocrine tumors that originate from neural crest-derived paraganglia and are considered to represent an extra-adrenal counterpart of pheochromocytoma. They can be found anywhere in the human body, from the base of the skull to the pelvis, along the embryologic migration routes of neural crest cells.[1] They can be familial or sporadic and predominantly affect women (female-to-male ratio, 2-3:1) between ages 40 and 60 years.[1,2] These tumors can be functional, producing hormones like adrenalin and noradrenalin that can cause transient or permanent hypertension. Measuring serum or urinary catecholamines and their end products, such as vanillylmandelic acid, can be helpful for the diagnosis of functional tumors.[3,4] Because of the potential for a hypertensive crisis and intraprocedural hemorrhage/bleeding, fine-needle aspiration (FNA) of these tumors is generally discouraged.

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See editorial on pages 417-418, this issue.

Received: August 20, 2020; **Revised:** August 27, 2020; **Accepted:** August 28, 2020

Published online November 24, 2020 in Wiley Online Library (wileyonlinelibrary.com)

DOI: 10.1002/cncy.22390, wileyonlinelibrary.com

All head and neck paragangliomas arise from parasympathetic paraganglia and account for 0.6% of all head and neck tumors. The most common location in this region is the carotid body, followed by the jugular bulb. Thyroid paragangliomas are extremely rare and are considered to be a subset of inferior laryngeal paragangliomas. As opposed to pheochromocytomas, most thyroid paragangliomas are nonfunctional and present as asymptomatic, solitary thyroid nodules that are often considered to be primary thyroid neoplasms and thus likely to be evaluated by FNA. These tumors pose a diagnostic challenge by cytologic and histologic evaluation not only because of their rarity in this anatomic location but also because of their morphologic overlap with benign and malignant thyroid neoplasms as well as metastatic neuroendocrine tumors.[5-9] In particular, the sclerosing variant of paraganglioma can have unusual morphology, with extensive sclerosis that may simulate an invasive malignant neoplasm.[10]

The objective of this study was to review the clinical presentation and cytomorphologic spectrum of thyroid paragangliomas and correlate these findings with histopathology on follow-up resection.

MATERIALS AND METHODS

A retrospective review of 5 thyroid paraganglioma FNA cases was performed. The cases were collected from the University of Pittsburgh Medical Center in Pennsylvania (n = 2); Catholic University Polyclinic Foundation, Rome, Italy (n = 1); Johns Hopkins Hospital, Baltimore, Maryland (n = 1); and Massachusetts General Hospital, Boston, Massachusetts (n = 1).

These FNAs were performed by radiologists or endocrinologists under ultrasound guidance. Rapid onsite evaluation was performed in 2 cases. Air-dried and alcohol-fixed direct smears were prepared from each pass until the material was deemed adequate for diagnosis or the procedure was terminated. The air-dried slides were stained with a Romanowsky-type stain (Diff-Quik), and the alcohol-fixed slides were stained with a Papanicolaou stain. Material was collected for liquid-based preparation (ThinPrep; Hologic Inc) in 3 cases. Cell blocks were not prepared for any of these cases. Aspirated material was collected for ancillary molecular studies for 2 cases in ThyroSeq *Preserve* medium (University of Pittsburgh Medical Center and Sonic Healthcare USA). The final cytology reports were signed out by board-certified cytopathologists. Follow-up surgical resection glass slides and/or digital slides (scanned at ×40 original magnification using an Aperio AT2 whole slide scanner; Leica) were reviewed for correlation with the FNA findings. Immunohistochemistry was performed on the surgical resection in all 5 cases with appropriate positive and negative controls.

The available metadata collected included patient demographics, radiology findings, and follow-up clinical information. Cytomorphology details, including the type of specimen preparation used, cellularity, pattern, cell size and shape, cytoplasm, nuclear features, and background were recorded as well as the Bethesda category and the final cytology diagnosis. Cytopathology-histopathology correlation was performed in all cases and the results of available ancillary tests (immunohistochemistry and molecular) were documented.

RESULTS

Clinical Findings

All patients were women (n = 5) and presented with an asymptomatic thyroid nodule. One case (case 3) was detected incidentally on a computed tomography scan of the head and neck region while working up this patient for a right vagus nerve schwannoma. The average age at presentation was 49 years (age range, 35-61 years). Radiologically, these nodules were well circumscribed, hypoechoic, and hypervascular, and they ranged in size from 1.8 to 3.0 centimeters. The nodules involved the left thyroid lobe (n = 4), with extension into the isthmus in 1 case, and the right thyroid lobe (n = 1). The clinical, radiologic, and available genetic test findings from FNA material are summarized in Table 1. Preoperative biochemical testing of serum or urine hormone levels was not performed because these patients were asymptomatic, except for 1 patient (case 5) who had had a history of hypertension. The clinical diagnosis of paraganglioma was not suspected in any of these cases. On postoperative follow-up, a complete clinical workup was negative for multicentric disease. In case 5, a small, partially calcified, portocaval mass was detected. Table 2 summarizes the FNA and surgical procedure details.

Cytopathology and Molecular Findings

The spectrum of cytopathologic findings is summarized in Tables 3 and 4. In case 2, an initial FNA was reported

TABLE 1. Clinical, Radiologic, and Genetic Findings in This Thyroid Paraganglioma Case Series

Case No.	Age, y	Sex	Clinical Presentation	Site	Size, cm	Ultrasound Findings	Multicentric	Genetic Test	Other Diagnoses
1	35	Woman	Asymptomatic thyroid nodule	Left thyroid lobe	1.8	Hypoechoic, vascular nodule	No	None	Chronic lymphocytic thyroiditis
2	61	Woman	Asymptomatic thyroid nodule	Left thyroid Lobe	3.0	Predominantly solid, hypoechoic, vascular nodule	No	SDHB mutation	Ovarian cancer, chronic lymphocytic thyroiditis
3	35	Woman	Incidentally detected on CT scan	Left thyroid lobe	2.0	Hypoechoic, irregular, hypervascular nodule	No	None	Vagus nerve schwannoma, chronic lymphocytic thyroiditis
4	55	Woman	Asymptomatic thyroid nodule	Isthmus and left lobe	3.0	Hypoechoic, vascular nodule	No	None	Micropapillary thyroid carcinoma, chronic lymphocytic thyroiditis
5	59	Woman	Asymptomatic thyroid nodule	Right thyroid lobe	3.0	Hypervascular, partially calcified, heterogeneous mass replacing much of the right lobe	No	None	Partially calcified portocaval mass

Abbreviation: CT, computed tomography.

TABLE 2. Summary of Cytology Procedures, Cytologic Diagnoses and Surgical Resections

Case No.	No. of FNA Passes	Slides Prepared	ROSE Diagnosis	Final Cytology Diagnosis	IHC on Cytology Material	FNA Complications	Follow-Up Surgery	Frozen Section Diagnosis	Final Histopathology Diagnosis	IHC on Resection	Operative Complications
1	2	4 smears	None	Follicular neoplasm (Bethesda category IV)	None	None	Total thyroidectomy	None	Paraganglioma	Yes	None
2	5	10 smears and 1 LBC	Adequate	Follicular neoplasm (Bethesda category IV)	None	None	Total thyroidectomy	None	Sclerosing paraganglioma with positive margins	Yes	Left vocal cord paralysis
3	2	4 smears and 1 LBC	None	AUS/FLUS (Bethesda category III)	None	None	Left lobectomy	Follicular lesion	Sclerosing paraganglioma with positive margin	Yes	None
4	8	17 smears	Adequate	Follicular neoplasm (Bethesda category IV)	Noncontributory[a]	None	Left lobectomy	Cellular thyroid lesion, defer to permanent	Paraganglioma	Yes	None
5	3	4 smears and 1 LBC	Adequate	Suspicious for follicular neoplasm (Bethesda category IV)	None	None	Right lobectomy	Suspicious for medullary thyroid carcinoma	Paraganglioma	Yes	Excess blood loss, right vocal cord paralysis

Abbreviations: AUS/FLUS, atypia of undetermined significance or follicular lesion of undetermined significance; FNA, fine-needle aspiration; IHC, immunohistochemistry; LBC, liquid-based cytology; ROSE, rapid onsite evaluation.

[a]Thyroglobulin and calcitonin stains were performed on smears with noncontributory results

TABLE 3. Spectrum of Cytoplasmic Cytomorphologic Findings in Thyroid Paragangliomas

Case No.	Cellularity	Cell Arrangement	Mimics Follicles	Glandular Features	Cell Size	Cell Shape	Cell Cytoplasm	Cell Granules	Cytoplasmic Borders
1	Hypercellular	Small, loose clusters; dispersed, isolated cells	Yes	No	Medium	Round-oval	Abundant, clear to vacuolated	No	Distinct
2	Hypercellular	Small, loose, and tight clusters; dispersed, isolated cells	Yes	No	Medium-large	Round-oval	Moderate, clear to eosinophilic to vacuolated	No	Indistinct to distinct
3	Hypocellular	Small, loose, and tight clusters; dispersed, isolated cells	Yes	No	Medium	Round-oval, spindle, and plasmacytoid	Moderate, eosinophilic	No	Indistinct to distinct
4[a]	Hypocellular	Small, loose clusters; dispersed, isolated cells	Not available	Not available	Not available	Not available	Not available	Not available	Not available
5	Hypocellular	Small clusters; dispersed, isolated cells	No	No	Medium	Oval and plasmacytoid	Moderate, eosinophilic	No	Indistinct

[a]Case 4 was an outside consult case and slides were unavailable for detailed repeat review.

as atypia of undetermined significance (AUS) with a negative ThyroSeq molecular test. A follow-up FNA for case 2 performed 6 months later was reported as a follicular neoplasm with a negative ThyroSeq molecular test but was positive for an SDHB mutation. For case 3, an initial FNA was nondiagnostic and was followed by a repeat FNA 2 months later with an AUS diagnosis. A ThyroSeq test was reported as indeterminate because of insufficient material. For case 5, in which an initial FNA was reported as AUS 3.5 months earlier, a repeat FNA was classified as suspicious for a follicular neoplasm.

FNA smears were hypocellular (n = 3) or hypercellular (n = 2). Smears showed clusters of loosely cohesive and isolated epithelioid cells with round-to-oval morphology, medium to large in cell size, and clear, amphophilic-to-foamy cytoplasm with indistinct cytoplasmic borders. Scattered plasmacytoid cells were present in 2 cases (Fig. 1). The nuclei were round to oval with focal nuclear membrane irregularities, grooves, inconspicuous nucleoli, and occasional intranuclear pseudoinclusions (Figs. 2 and 3). Scattered cells with marked anisonucleosis were present in all cases (Fig. 4). Naked nuclei were present in 4 cases. Variable binucleated and multinucleated giant cells were also present. The background showed blood vessels (Fig. 5), erythrocytes, and lymphocytes without colloid or amyloid. A few possible sustentacular cells with oval, elongated, curved naked nuclei were present in 2 cases. The sclerosing variant showed tight, cohesive clusters of spindle-to-epithelioid cells with overlapping nuclei on liquid-based preparation (Fig. 6). The cytopathology diagnoses rendered were follicular neoplasm (n = 3), suspicious for follicular neoplasm (n = 1), and AUS/follicular lesion of undetermined significance (n = 1).

Histopathology Findings

All thyroid lesions were surgically excised. The final surgical diagnoses were paraganglioma (n = 3) and sclerosing paraganglioma with invasive features (n = 2). Intraoperative frozen section diagnoses were available for 3 cases and were reported as follows: case 3, follicular lesion; case 4, cellular lesion, defer to permanent section; and case 5, suspicious for medullary thyroid carcinoma (MTC). For cases 1, 4, and 5 (Fig. 7A-C), the histopathology was similar to that of pheochromocytoma or other anatomic site paragangliomas. These tumors were composed of nests of tumor cells (Zellballen) or were growing in a trabecular pattern associated with a prominent vascular

TABLE 4. Spectrum of Nuclear Cytomorphologic and Background Findings in Thyroid Paragangliomas

Case No.[a]	N:C Ratio	Nuclear Atypia	Nuclear Irregularities	Intranuclear Pseudoinclusions	Nucleoli	Naked Nuclei	MNG Cells	Colloid	Melanin	Necrosis/ Mitoses	Background	Blood Vessels
1	Low	Yes	Yes	No	None	Few	Yes	None	No	No	Lymphocytes, monocytes	Yes, many
2	Low	Yes	Focal	Yes	Focal	Many	Yes	None	No	No	Possible sustentacular cells, lymphocytes, blood	Yes, many
3	Low	Yes	Focal	No	Focal	Few	Yes	None	No	No	Possible sustentacular cells, lymphocytes, blood	Yes
5	Low	Yes	No	No	None	Few	None	None	No	No	Blood	Yes

Abbreviations: MNG, multinucleated giant cell; N/C, nuclear:cytoplasmic ratio.
[a]Case 4 was an outside consult case and slides were unavailable for detailed repeat review.

Figure 1. A fine-needle aspiration smear shows dispersed, medium-to-large cells, including scattered, isolated plasmacytoid cells with moderate-to-abundant cytoplasm and round-to-oval nuclei exhibiting anisonucleosis. Note the focal, loose clusters of cells mimicking follicles (open arrow), occasional sustentacular cells (black arrows) with elongated nuclei, and several naked nuclei in the background (Diff-Quik stain, original magnification ×400).

Figure 2. A fine-needle aspiration reveals loosely cohesive clusters of epithelioid cells with oval nuclei, focal conspicuous nucleoli, and mildly irregular nuclear contours (Papanicolaou stain, original magnification ×400).

network. The cells were round to oval with abundant, granular, eosinophilic or basophilic cytoplasm. The nuclei were round to oval with scattered, severe anisonucleosis. Occasional giant multinucleated cells were observed. Rosettes, acini, melanin pigment, necrosis, mitoses, and vascular or capsular invasion were not present.

Cases 2 and 3 showed features of the sclerosing variant of paraganglioma (Fig. 8A-D). In these 2 cases, on gross examination of the resected thyroid specimen, the cut surface revealed a solid, pink-tan, ill-defined mass. Histopathology of the sclerosing variant of paraganglioma

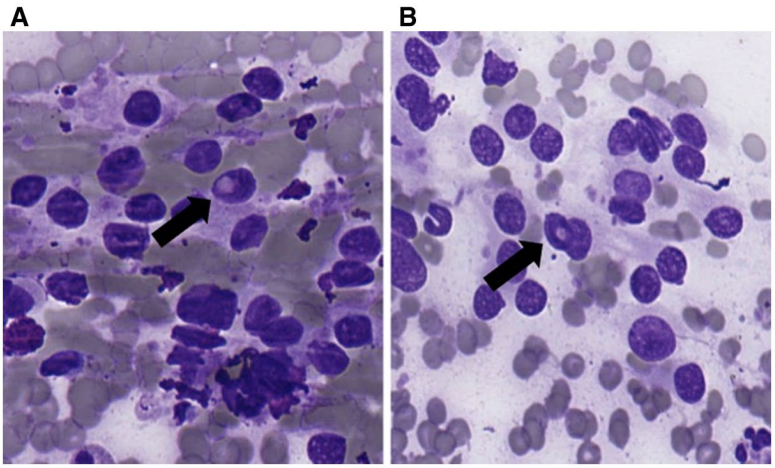

Figure 3. (A,B) Fine-needle aspiration smears reveal epithelioid cells with (arrows) round-to-oval nuclei and intranuclear pseudoinclusions (Diff-Quik stain, original magnification ×400).

was characterized by a focal, nested Zellballen growth pattern admixed with irregular, highly sclerotic, and vascularized bands of stroma separating tumor nests. The tumor cell nuclei in these sclerosing tumors showed focal nuclear atypia, including some large cells with prominent nucleoli and scattered, hyperchromatic nuclei. The cells were spindle to epithelioid and their cytoplasm was clear to granular and foamy, imparting a histiocytoid appearance. Infiltrative growth was evident as extensive sclerosis at the periphery, with positive surgical resection margins and involvement of perithyroidal skeletal muscle. Unlike conventional paragangliomas, the thick sclerotic and fibrous bands of sclerosing paragangliomas imparted the appearance of desmoplastic stroma typically seen with invasive malignant neoplasms. Rare, atypical mitoses were present in 1 case. Both cases of sclerosing paraganglioma exhibited scattered tumor-infiltrating lymphocytes but no necrosis, and no capsular or vascular invasion was present. Background chronic lymphocytic thyroiditis was present in 4 cases. Case 4 also had an incidental papillary microcarcinoma (0.2 cm).

Immunohistochemistry Findings

Immunohistochemistry was performed on all 5 surgical resection specimens. The tumor cells were positive for synaptophysin and/or chromogranin. S-100 highlighted the sustentacular cells and nearby nerves, and CD34 highlighted the rich tumor vascular network. The tumor cells were negative for pancytokeratin, thyroid transcription factor 1 (TTF-1), thyroglobulin, calcitonin, carcinoembryonic antigen (CEA) and Hector Battifora mesothelioma (HBME). Case 2 showed loss of SDHB by immunohistochemistry.

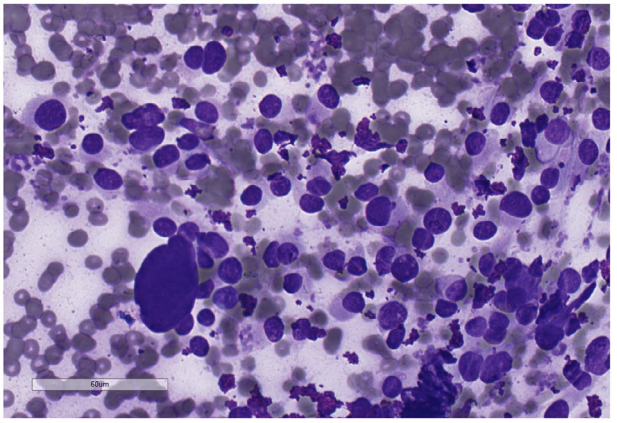

Figure 4. A fine-needle aspiration smear exhibits several naked nuclei stripped of cytoplasm and marked anisonucleosis (Diff-Quik stain, original magnification ×400).

Follow-Up

For case 1, the patient did well, without any recurrence or metastatic disease 7 years after surgery. In case 2, the patient developed temporary postoperative laryngeal nerve paralysis and hoarseness that resolved after 6 months. For this patient, at follow-up ultrasound 8 years after surgery, a 0.6-cm possible remnant was discovered in the thyroid bed that is being followed radiologically because of its small size for further investigation. For cases 3, 4, and 5, the patients all did well, without recurrence or metastatic

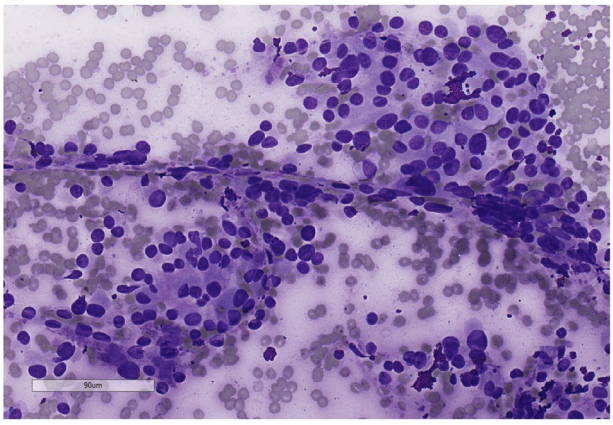

Figure 5. A direct smear shows a transgressing blood vessel surrounded by plasmacytoid cells with amphophilic cytoplasm and indistinct cell borders (Diff-Quik stain, original magnification ×400).

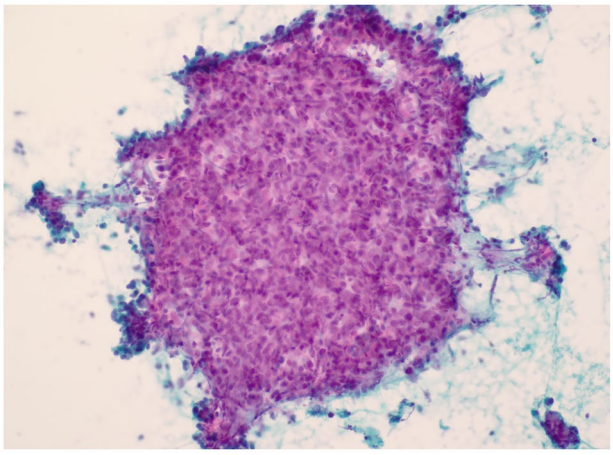

Figure 6. This ThinPrep slide of a fine-needle aspiration sample obtained from a sclerosing paraganglioma shows a tight, cohesive cluster of cells with mildly overlapping oval nuclei (Papanicolaou stain, original magnification ×400).

disease even up to 9 years after surgery. In case 5, the patient's hypertension was not resolved after surgical resection, confirming the nonfunctional nature of her thyroid paraganglioma.

DISCUSSION

Thyroid paragangliomas, because they are very rare neoplasms in this anatomic location, are usually misdiagnosed by FNA. In our series, all cases were misdiagnosed by cytology (5 of 5 cases) as well as at frozen section (3 of 3 cases). Normal paraganglia act as chemoreceptors and thereby play an important role in homeostasis by secreting catecholamines in response to stress. Paraganglia are made up of 2 cell types: type 1 (chief) and type 2 (sustentacular) cells. Type 1 cells contain cytoplasmic granules filled with catecholamines, whereas type 2 cells act as supporting cells. Paraganglia can also be categorized into 2 physiologic groups: 1) parasympathetic, arising mostly in the head and neck region, which are usually nonfunctional, and 2) sympathetic, arising in the retroperitoneum, mediastinum, or pelvis, which are usually functional.[1,2,11] Paragangliomas may arise from these paraganglia and are typically benign, slow-growing tumors. Possible etiologies for their development include chronic hypoxic exposure and heritable causes, such as mitochondrial complex II defects. In our series, 4 of the 5 cases also had chronic lymphocytic thyroiditis. The significance of this association is unknown and, to the best of our knowledge, has not been previously reported in the literature.

Although most paragangliomas are sporadic, a significant number of cases can be familial. The familial syndromic cases tend to be multicentric and prone to recurrence. Hence germline mutation testing is recommended for all patients with paragangliomas. A positive family history is found in 10% to 25% cases, with germline mutations in SDHD, SDHB, and SDHC. Although SDHD mutation is the most common, SDHB is associated with a poorer prognosis. In our small series, SDHB mutation was detected in 1 patient (case 2), and it is interesting to note that this was the only patient who had a possible local recurrence. Occasional cases may also be observed in association with von Hippel-Lindau disease, multiple endocrine neoplasia type 2 (MEN2), and neurofibromatosis, as well as Carney triad (gastrointestinal stromal tumor, paraganglioma, and pulmonary chondroma).[12,13] Head and neck paraganglia, including those located in the thyroid, typically lack endocrine activity, except for the carotid body paraganglia, which possess endocrine activity and contain catecholamines. Consequently, they often present as asymptomatic, slow-growing masses in the neck without a hypertensive crisis or circulating catecholamines.

On the basis of limited published cases, the clinical course of thyroid paragangliomas varies, with the majority behaving in a benign fashion and occasionally with local aggressive behavior.[14,15] In our small series, the

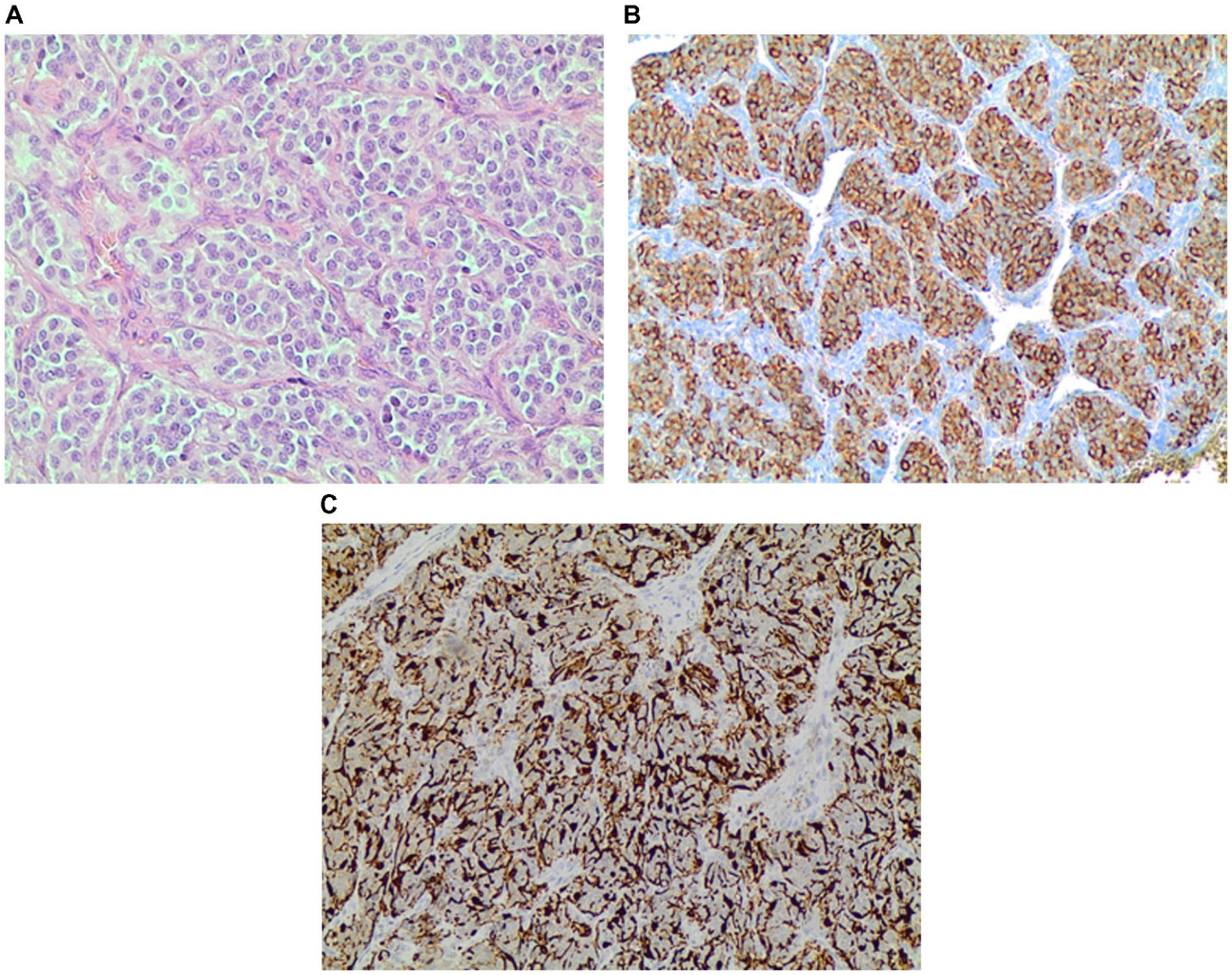

Figure 7. Resected paraganglioma morphology is illustrated. (A) Nests of chief cells are shown arranged in an alveolar (Zellballen) pattern with a rich intervening capillary network (H&E stain, original magnification ×400). (B) Chief cells are positive for chromogranin A (immunohistochemistry, original magnification ×200). (C) Sustentacular cells are positive for S-100 protein (immunohistochemistry, original magnification ×200).

clinical outcomes after surgery were all favorable. Only 3 case reports of malignant paraganglioma of the thyroid have been described in the literature.[16-18] Surgical resection is the treatment of choice for symptomatic thyroid paragangliomas, after which patients require prolonged follow-up with imaging. Although FNA of a paraganglioma is allegedly contraindicated, it can be performed if biochemical screening for catecholamine secretion is negative and the patient is prepared with α-adrenergic blockade. Because the preoperative diagnosis was not suspected in any of our cases, FNA was performed without such blockade. Fortunately, the tumors in our series were nonfunctional and the FNA procedures occurred without any acute adverse event.

The cytopathologic features of thyroid paragangliomas are similar to those of paragangliomas at other anatomic sites. These features overlap with primary benign and malignant neoplasms of the thyroid gland, parathyroid neoplasms, and metastatic neuroendocrine tumors, leading to diagnostic challenges.[19-21] In our series, most FNA specimens were misdiagnosed as a follicular neoplasm. This was likely attributed to their pattern of loosely cohesive clusters of round cells that mimicked follicles. The unique constellation of cytologic features evident in our series that may be diagnostically helpful include clusters of round epithelioid cells in association with focal, marked anisonucleosis, sustentacular cells, naked (stripped) nuclei, and the absence of background

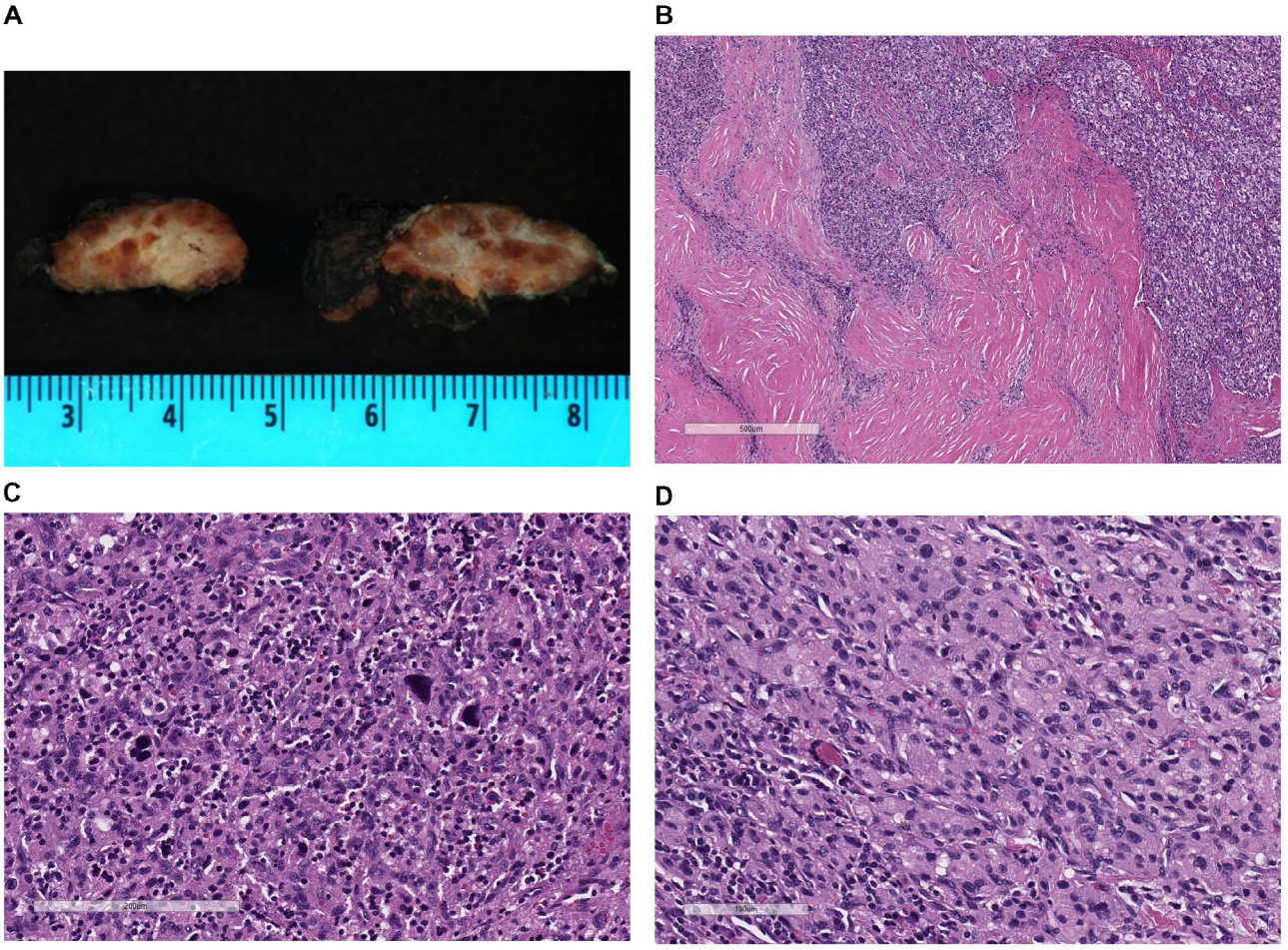

Figure 8. Resected sclerosing paraganglioma morphology is illustrated. (A) This gross image of a sclerosing paraganglioma shows a tan-yellow, poorly circumscribed nodule surrounded by brown-to-beefy red, normal thyroid parenchyma. (B) Irregular cords of tumor cells are surrounded by extensive sclerotic stroma simulating an invasive malignant neoplasm (H&E stain, original magnification ×4). (C) A tumor region exhibits typical nests of epithelioid tumor cells with clear-to-eosinophilic, granular cytoplasm (H&E stain, original magnification ×400). (D) Another tumor region shows scattered, large, hyperchromatic nuclei (H&E stain, original magnification ×200).

colloid or amyloid. Thyroid paragangliomas may also be misdiagnosed as MTC because of the presence of plasmacytoid or spindle cells, multinucleated giant cells, and intranuclear inclusions. Collecting material for cell blocks to perform immunohistochemistry is essential for reaching the correct diagnosis (Table 5), in addition to measuring serum calcitonin and CEA levels. On immunohistochemistry, both paragangliomas and MTC show expression of neuroendocrine markers. However, MTC would also be positive for calcitonin and CEA. Furthermore, a Congo Red stain for suspected amyloid would only be positive in MTC. It is important to note that the paraganglioma-like variant of MTC would be negative for calcitonin, complicating the distinction.[22]

In hyalinizing trabecular tumor (HTT), also known as paraganglioma-like adenoma of thyroid, the cytopathology is characterized by small, loose clusters or syncytia of bipolar or triangular cells. The follicular cells in HTT often have more filamentous cytoplasm, with long cytoplasmic processes surrounding amorphous basement membrane material. The nuclei in HTT are round to elliptical with smooth borders, they have even chromatin, and they can have intranuclear inclusions and grooves. The amorphous basement membrane material can mimic amyloid of MTC. On immunohistochemistry, HTT is positive for TTF-1, thyroglobulin, and paired box 8 (PAX-8) and shows membranous expression of Ki-67.[23] Intranuclear

TABLE 5. Immunohistochemistry in the Differential Diagnosis of Thyroid Paragangliomas

Immunomarker	Paraganglioma	MTC	Follicular Lesion	HTT	PTC
Cytokeratin	–	–	+/–	+	+ (CK-19)
Chromogranin A	+	+	–	+	–
Calcitonin	–	+	–	–	–
CEA	–	+	–	–	–
Galectin-3	–	+	–	–	+
HBME	–	–	–	–	+
Ki-67	Variable	Variable	Variable	Membranous	Variable
Parathormone	–	–	–	–	–
Synaptophysin	+	+	–	–	–
S-100	+ (Sustentacular cells only)	–	–	–	–
TTF-1/PAX-8	–	+ (Weak)	+	+	+
Thyroglobulin	–	+	+	+	+

Abbreviations: –, negative; +, positive; CEA, carcinoembryonic antigen; CK, cytokeratin; HBME, Hector Battifora mesothelioma; HTT, hyalinizing trabecular tumor; MTC, medullary thyroid carcinoma; PAX, paired box; PTC, papillary thyroid carcinoma; PTH, parathyroid hormone; TTF-1, thyroid transcription factor 1.

pseudoinclusions could also confuse a paraganglioma with papillary thyroid carcinoma. However, cytologic features such as papillary fragments, nuclear grooves, psammoma bodies, and dense gum-like colloid would help support the diagnosis of papillary thyroid carcinoma.[24] On immunohistochemistry, papillary thyroid carcinoma would be positive for TTF-1, thyroglobulin, PAX-8, CK19, and HBME, whereas paraganglioma would be negative.[23]

Of note, most thyroid paragangliomas may also be misdiagnosed on intraoperative frozen sections as follicular carcinoma, Hurthle cell carcinoma, MTC, metastatic carcinoma, or they may end up being deferred.[25,26] Three cases in our series that had an intraoperative frozen section were incorrectly reported as a follicular lesion, cellular lesion best deferred to permanent sections, and suspicious for MTC. Like cytology, conventional paragangliomas show histopathology similar to that of paragangliomas in other anatomic sites. Unusual morphologic variants, such as the sclerosing variant,[10,27,28] can exhibit a hemangiopericytoma-like appearance and show clear cell changes as well as spindling of cells. Sclerosing paragangliomas can be symptomatic, sometimes causing airway occlusion, as reported by Mukhopadhyay et al.[10] The presence of extensive sclerosis may simulate an invasive histologic growth pattern that mimics malignancy. The sclerosing variant is also known for recurrence. The differential diagnosis of sclerosing paraganglioma in the thyroid includes fibrous variant of Hashimoto thyroiditis, Reidel thyroiditis, immunoglobulin G4-related thyroid disease, papillary thyroid carcinoma with nodular fasciitis-like stroma, mesenchymal neoplasms (eg, solitary fibrous tumor, fibromatosis), or metastatic neoplasms with desmoplasia that may warrant ancillary tests to confirm their diagnosis. Although the presence of nuclear atypia, vascular invasion, and perineural invasion can be seen with paragangliomas, these findings do not predict malignant behavior. Only focal nuclear pleomorphism was identified in some of our cases. Nevertheless, true malignancy for paragangliomas is defined by virtue of metastasis to a nonendocrine location, such as cervical lymph nodes, lungs, or liver.

In summary, although our cohort is limited to 5 cases, this series represents the largest collection to date characterizing the cytomorphology of thyroid paragangliomas with histopathologic correlation. In all cases, thyroid paragangliomas were misdiagnosed on FNA as follicular neoplasms, both because of the rarity of these tumors in this location and because their cytomorphology mimics follicular-patterned clusters without background colloid. The presence of naked nuclei, focal marked anisonucleosis, and sustentacular cells and the absence of colloid are important cytologic clues that may help to triage FNA samples for ancillary testing to confirm the diagnosis.

FUNDING SUPPORT

No specific funding was disclosed.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

All authors were equally involved in the conceptualization, review, writing, and editing of this article.

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