Thyroid Paraganglioma

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Thyroid paragangliomas are rare tumors that arise from the inferior laryngeal paraganglia. Most patients are female and present with an asymptomatic thyroid nodule. Histologically, the tumor is composed of cells arranged in a well-defined nest (zellballen) pattern surrounded by a thin fibrovascular stroma. It is a diagnostic pitfall and is occasionally misdiagnosed as follicular neoplasm, medullary thyroid carcinoma, intra-thyroid parathyroid proliferation, and especially secondary neuroendocrine tumors. Immunohistochemical stains (cytokeratin, parathyroid hormone, thyroid transcription factor 1, tyrosine hydroxylase, chromogranin A, synaptophysin, S100, calcitonin, hormone, thyroid transcription factor 1, tyrosine hydroxylase, chromogranin A, synaptophysin) are essential in establishing the diagnosis. Loss of succinate dehydrogenase complex, subunit B (SDHB), immunexpression can be used to triage genetic testing because some mutations are associated with a higher risk for developing metastasis. Total thyroidectomy or lobectomy for solitary lesion is the preferred treatment. Elective lymph node dissection is usually not indicated. Postoperatively, patients should receive hormonal evaluation for functional disease and imaging for evaluation of multifocal or metastatic disease.


Paragangliomas are uncommon neuroendocrine tumors, arising from the neural crest-derived paraganglia of the autonomic nervous system. Paraganglioma adjacent to or inside the thyroid gland is a subset of laryngeal paragangliomas, which was first described in the right upper lobe of the thyroid gland by Van Miert in 1964. Because thyroid paragangliomas arise from the inferior laryngeal paraganglia, one theory is that as paraganglioma develops from the inferior laryngeal paraganglia, it is slowly pulled downward and eventually rests lateral to the thyroid gland. It is also probable that the inferior laryngeal paraganglia may form within the thyroid capsule, which could eventually develop into an intrathyroidal paraganglioma.

CLINICAL PRESENTATION

Thyroid paraganglioma has a strong female predominance, and the mean age of presentation is 48 years. Most patients are asymptomatic, with a nonfunctional thyroid nodule for several years discovered incidentally with radiographic imaging. In the few symptomatic patients, their presentation ranged from an anterior neck mass, dysphagia, dyspnea, stridor, and hemoptysis. The reported incidence of functional paragangliomas is only 1% to 3% in the head and neck, with a single case report of functional thyroid-associated paraganglioma. The catecholamine profile of paraganglioma depends on the anatomic location and genotype of the tumor. Paragangliomas located in the skull base, head and neck, and thyroid are associated with the parasympathetic nervous system, which often lacks tyrosine hydroxylase (the rate-limiting step in dopamine synthesis). Hence, they usually present with minimal or no catecholamine synthesis (nonsecreting), resulting in clinically asymptomatic presentation. In contrast, paragangliomas located in the thoracolumbar area are associated with the sympathetic nervous system, and they tend to secrete catecholamines. Hence, hypertension, palpitation, sweating, and episodic headaches are often some of the clinical presentations. Occasional VHL, TMEM127, and SDHA-related head and neck paragangliomas have been described in the literature. However, most familial disease in the head and neck paraganglioma is associated with SDHD, SDHC, SDHB, and SDHAF2 mutations. Although the biochemical phenotype of SDHAF2 is still unknown, the biochemical phenotype of the other genes are either nonsecreting or secreting dopamine, epinephrine, norepinephrine, metanephrine, normetanephrine, and methoxytyramine (Table). Tumors with the same mutation can be either functional or nonfunctional depending on whether they are located in the head and neck or the abdomen. Catecholamine synthesis starts with the amino acid tyrosine, which is converted to dopamine in the presence of tyrosine hydroxylase. Tyrosine hydroxylase is the rate-limiting step in catecholamine synthesis. In the storage vesicles of noradrenergic nerves and chromaffin cells, dopamine β-hydroxylase converts dopamine to norepinephrine. In the adrenal medulla, norepinephrine is converted to epinephrine in the presence of phenylethanolamine-N-methyltransferase. Although most epinephrine originates from the adrenal medulla, this reaction can also occur in some extra-adrenal sympathetic paraganglia. Catechol-O-methyltransferase (COMT) converts norepinephrine to normetanephrine, epinephrine to metanephrine, and dopamine to methoxytyramine in the adrenal medulla, extraneuronal tissue, or nonneuronal cells, respectively. Hence, it is recommend-
ed that all patients with newly diagnosed paraganglioma should receive a biochemical workup for catecholamine excess and their O-methylated metabolites (normetanephrine, metanephrine, and methoxytyramine). 15, 16 Most patients with thyroid paragangliomas are euthyroid, 17 although normal calcitonin and carcinoembryonic antigen (CEA) levels 18 and are negative for antiperoxidase, parathyroid hormone, and antithyroglobulin antibodies in their serum. 16 Previously reported cases of thyroid paragangliomas were detected as a cold nodule on thyroid scintigraphy and a hypoechoic or heterogeneous nodule with increased intranodular and perinodular vascular flow on ultrasonographic color Doppler analysis. 4 Although most thyroid paragangliomas are confined to the thyroid gland, they infrequently invade into adjacent vessels, nerves, esophagus, trachea, and larynx. 3, 16 Although thyroid paraganglioma can be solitary on initial presentation, approximately 14% of patients also had disease in either the carotid body or vagal paraganglia. 3 Hence, follow-up imaging should include computed tomography or magnetic resonance imaging of the neck, chest, and abdomen/pelvis. 16 The use of 18F-6-fluorodihydroxyphenylalanine positron emission tomography has been described as the most valuable functional-imaging modality for localization of succinate dehydrogenase related to head and neck paragangliomas. 17 Follow-up imaging should occur relatively soon after initial surgery so that concurrent disease can be identified and not confused with metastatic or recurrent disease. 4

**HISTOPATHOLOGY**

**Gross Features**

Most thyroid paragangliomas are solitary nodules. They are usually large, well-circumscribed, partially to completely encapsulated solid tumors with tan–gray cut surface (Figure 1). Rare cases have described an infiltrating growth pattern with a direct extension into cricoideal cartilage, trachea, subglottic larynx, and esophagus. 3, 10, 15

**Microscopic Features**

Histologically, thyroid paraganglioma is a well-delineated tumor surrounded by a thin, fibrous capsule (Figure 2). The tumor typically shows an organoid zellballen architecture seen in paraganglioma elsewhere in the body. 3 The tumor is composed of 2 cell types: chief cells, which have pale eosinophilic cytoplasm, round to oval nuclei, and finely granular chromatin, and sustentacular cells, which have spindled-shaped nuclei and scant cytoplasm (Figure 3). Although mild to moderate nuclear pleomorphism may occasionally be present, mitotic figures are usually rare. Neoplastic chief cells are usually positive for neuroendocrine markers, such as chromogranin A, synaptophysin, and neuron-specific enolase, but are negative for cytokeratins, CAM 5.2 (Figure 4), parathyroid hormone, calcitonin, CEA, thyroglobulin, and thyroid transcription factor 1 (TTF-1). Given that tyrosine hydroxylase is the rate-limiting step in catecholamine synthesis, staining for tyrosine hydroxylase will be supportive of the diagnosis. 3 However, the tyrosine hydroxylase (Figure 5) and chromogranin A (Figure 6) immunoreactivity is usually weaker, more variable, and can occasionally be negative in parasympathetic paragangliomas, when compared with their sympathetic counterpart. 3 Glial fibrillary acidic protein and S100 (Figure 7) staining usually highlights compressed sustentacular cells, which are located at the periphery of the tumor nests. No amyloid depositions or C-cell hyperplasias are identified in the surrounding follicular tissue. Some cases of thyroid paragangliomas showing extensive fibrosis within the tumor or surrounding tissue were reported as sclerosing thyroid paraganglioma. 18

**MOLECULAR GENETICS**

Paragangliomas and pheochromocytomas are tumors derived from the extra-adrenal paraganglia or adrenal medulla, respectively. Although most of these tumors are considered sporadic, to date, approximately 30% to 40% are associated with at least 14 known susceptibility genes (MEN1, NF1, RET, VHL, SDHA, SDHB, SDHC, SDHD, SDHAF2, TMEM127, EGLN1, HIF2A, KIF1Bβ, and MAX). 8, 19 Up to 30% of all head and neck paragangliomas are hereditary and are associated with different tumor syndromes. 3 Major hereditary disorders associated with paraganglioma or pheochromocytoma are multiple endocrine neoplasia, von Hippel–Lindau disease, neurofibromatosis, and familial paraganglioma syndromes 1 to 4. The paraganglioma syndromes caused by mutations of the succinate dehydrogenase (SDH) genes make up most of the familial cases. 8 Paraganglioma 1 is associated with mutation of the succinate dehydrogenase complex, subunit D gene (SDHD); paraganglioma 2 with mutation in the SDH5/SDHAF2 gene; paraganglioma 3 with mutation in the SDHC gene; and paraganglioma 4 with mutation in the SDHB gene. 8 Succinate dehydrogenase enzyme (SDH) complex is composed of 4 subunits encoded by 4 succinate dehydrogenase genes, namely, SDHA, SDHB, SDHC, and SDHD. These 4 subunits are crucial to the Krebs cycle as part of the mitochondrial complex II in the aerobic electron transport of the respiratory chain. Because the mitochondrial complex II is believed to function as a tumor

<table>
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<tr>
<th>Gene</th>
<th>Association With Head and Neck Paraganglioma</th>
<th>Biochemical Phenotype</th>
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<tr>
<td>VHL</td>
<td>+/−</td>
<td>NMN, NE</td>
</tr>
<tr>
<td>NF1</td>
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<td>−</td>
<td>E, MN, MNMN</td>
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<td>MN</td>
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<tr>
<td>SDHAF2</td>
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</tr>
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Abbreviations: +, yes; −, no; DA, dopamine; E, epinephrine; HIF2A, hypoxia-inducible factor-2α; MAX, MYC associated factor X; M, metanephrine; MT, methoxytyramine; NE, norepinephrine; NF1, neurofibromin 1; NMN, normetanephrine; NS, nonsecreting; RET, ret proto-oncogene; SDHA, succinate dehydrogenase complex, subunit A, flavoprotein; SDHAF2, succinate dehydrogenase complex assembly factor 2; SDHB, succinate dehydrogenase complex, subunit B, iron sulfite; SDHC, succinate dehydrogenase complex, subunit C, integral membrane protein; SDHD, succinate dehydrogenase complex, subunit D, integral membrane protein; TMEM127, transmembrane protein 127; VHL, von Hippel–Lindau tumor suppressor.

* Because of the rapidly expanding spectrum of biochemical findings and new data being accrued, these biochemical phenotypes are current to May 2014.
suppressor, when it becomes defective, it gives rise to the overexpression of several hypoxia-inducible genes that are believed to result in proliferation of paraganglia.\textsuperscript{20} Multiple head and neck paragangliomas and the occurrence of head and neck paragangliomas together with pheochromocytomas are more commonly seen in SDHD and SDHB mutation carriers. SDHC can also be seen in that context. The risk for the development of malignancy is significantly higher in patients with SDHB mutations, compared with patients with SDHC and SDHD mutations or those with sporadic tumors.\textsuperscript{21} Therefore, it has been recommended that patients with an SDHB mutation be screened for local and systemic metastatic disease.\textsuperscript{22} Loss of immunoreactivity to SDHB protein has been seen in paraganglioma/pheochromocytoma with SDHA, SDHB, SDHC, SDHD, or SDHAF2 mutations, which presumably results from destabilization and degradation of the SDH complex, which is assembled from 4 separately coded subunits, when any of those subunits is mutated. Hence, a surrogate marker for some of the familial paraganglioma syndromes caused by SDH mutations is the loss of SDHB immunoreactivity.\textsuperscript{22} A negative SDHB staining indicates the presence of a mutation and a positive staining indicates the absence of mutation (Figure 8). The immunohistochemical stain for SDHB has also provided prognostic data because of the high rate of malignancy associated with SDHB-driven paragangliomas. An immunohistochemical stain for SDHA can be used to demonstrate the presence of SDHA germline mutation.\textsuperscript{23}

Paragangliomas associated with a germline SDHA mutation show negative staining with SDHA as well as SDHB.\textsuperscript{14} Hereditary pheochromocytoma or paraganglioma show distinct profiles of gene expression and are divided according to their profiles into 2 clusters.\textsuperscript{20} Cluster 1 includes tumors carrying the VHL and SDHA, SDHB, SDHC, SDHD, and SDHAF2 mutations and display signatures of pseudohypoxia, angiogenesis, increased reactive oxygen species, and reduced oxidative response, resulting in changes in the cell metabolism. Cluster 2 consists of tumors caused by susceptibility genes rich in kinase receptor signaling and downstream pathways, such as RAS signaling (RET and NF1), mitogenesis (MAX), and protein trafficking (TMEM127), and are implicated in adrenergic metabolism, protein synthesis, and kinase signaling. In the future, understanding the specific genetic alterations may lead to

\textbf{Figure 1.} Cut section of the thyroid gland showing a large, well-circumscribed tumor with a tan-gray surface.

\textbf{Figure 2.} Photomicrograph showing a thinly encapsulated tumor with zellballen architecture (hemotoxylin-eosin, original magnification ×4).

\textbf{Figure 3.} Photomicrograph showing chief cells with pale eosinophilic cytoplasm and round to oval nuclei surrounded by sustentacular cells (hemotoxylin-eosin, original magnification ×20).

\textbf{Figure 4.} Photomicrograph showing chief cells, which are nonimmunoreactive for CAM 5.2 (original magnification ×20).
the development of molecular targeted therapies, which could be beneficial in patient management.9

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for thyroid paraganglioma includes the following tumors: follicular neoplasm, metastatic renal cell carcinoma, metastatic neuroendocrine tumor, medullary thyroid carcinoma, hyalinizing trabecular tumor, and intrathyroid parathyroid proliferation. Follicular neoplasms are characterized by follicular cells arranged in a microfollicular, solid to trabecular pattern enclosed by a distinct capsule. The architectural pattern and cytologic features are different from those of the surrounding thyroid tissue. The presence of capsular and/or vascular invasion will differentiate follicular carcinoma from follicular adenoma in the absence of diagnostic nuclear features of papillary carcinoma. These tumors are strongly immunoreactive with thyroglobulin, TTF-1, and low–molecular-weight cytokeratin. Renal cell carcinoma, one of the most-common extrathyroidal tumors to metastasize to the thyroid gland, consists of clear cells with round nuclei and prominent nucleoli, arranged in a solid, alveolar, and acinar pattern, surrounded by delicate thin-walled blood vessels. Metastatic renal cell carcinoma shows a lack of immunoreactivity for thyroglobulin and TTF-1 but shows immunoreactivity for cytokeratin, CD10, and vimentin. Metastatic neuroendocrine carcinoma to the thyroid gland can have similar histologic features as that of thyroid paraganglioma. The clinical history, the presence of a predominantly interstitial pattern of spread, an occurrence of multiple tumor foci, tumor cells that form subepithelial ball-like collections (folliculotropism), rosette formations with lumen, and a lack of immunoreactivity for calcitonin and CEA favor a metastatic neuroendocrine tumor.24 Hyalinizing trabecular tumor, formerly designated paraganglioma-like adenoma of the thyroid, can simulate thyroid paraganglioma because of its histologic resemblance to a neuroendocrine tumor.25 Morphologically, they are well-delineated tumors characterized architecturally by a solid, trabecular, and nested pattern. The tumor cells are polygonal to elongated and have round nuclei and abundant eosinophilic or amphi-
philic cytoplasm with occasional oval eosinophilic nucleoli arranged in nests separated by bands of hyaline material. The overlapping nuclear features of a hyalinizing trabecular tumor and papillary thyroid carcinoma, such as pseudoinclusions and longitudinal grooves, are relatively common. The characteristic feature of a hyalinizing trabecular tumor is abundant hyaline material that is intratrabecular and interstitial. The extracellular hyaline material can be misinterpreted as amyloid but would be negative for Congo red stain. A hyalinizing trabecular tumor is strongly immunoreactive for thyroglobulin and TTF-1, and the neuroendocrine markers are usually negative. Differentiating thyroid paraganglioma from medullary thyroid carcinoma is extremely important because of the difference in prognosis and treatment. Medullary thyroid carcinomas have a strong tendency to metastasize to the surrounding cervical lymph nodes. Complete resection of the tumor with or without cervical lymph node dissection, external radiation, and close clinical follow-up for monitoring recurrence or metastasis are routinely performed for patients with medullary thyroid carcinoma. However, only complete resection of the tumor is recommended for patients with thyroid paraganglioma. The histologic features of medullary thyroid carcinoma are sheets, nests, or trabeculae of polygonal, round, or spindle cells, separated by varying amount of fibrovascular stroma and amyloid deposits. Morphologically, it can be difficult to differentiate thyroid paraganglioma from medullary carcinoma. In medullary carcinoma, the tumor cells are immunoreactive for cytokeratin, TTF-1, neuroendocrine markers, calcitonin, and CEA. In contrast, paragangliomas are negative for cytokeratin, TTF-1, calcitonin, and CEA. Paraganglioma-like medullary carcinoma, a rare subtype of medullary thyroid carcinoma, is also in the differential diagnosis. It is characterized as an encapsulated tumor with a trabecular and insular growth pattern. The tumor cells are polygonal, with distinct cell borders; fine, granular eosinophilic cytoplasm; and round to oval nuclei, separated by capillary-rich stroma. Mitotic activity is absent. Paraganglioma-like medullary thyroid carcinomas show strong immunoreactivity for cytokeratins, calcitonin, chromogranin, synaptophysin, and CEA but are negative for both thyroglobulin and TTF-1. Interestingly, spindle-shaped and stellate cells with strong S100 immunoreactivity can intermingle with the tumor cells. Lastly, intrathyroid parathyroid proliferations are immunoreactive with AE1/AE3, parathyroid hormone, and chromogranin and are negative for tyrosine hydroxylase, thyroglobulin, and calcitonin.

**TREATMENT AND PROGNOSIS**

Surgical excision is the treatment of choice for thyroid paragangliomas. Depending on the size, number of tumor foci, and extent of involvement, different options range from subtotal thyroidectomy to total thyroidectomy. The benefit of radiation therapy is controversial. Initial screening for serum calcitonin and CEA levels may be helpful in excluding a diagnosis of medullary carcinoma. However, its value in monitoring residual/recurrent disease is unwarranted. There are no unequivocal histologic or immunohistochemical markers that distinguish benign from malignant paragangliomas. Per 2004 World Health Organization criteria, malignancy in paraganglioma or pheochromocytoma is defined by the presence of metastasis to sites where paraganglionic tissue is not normally present. Cervical lymph nodes are the most common site of regional spread, whereas lung, liver, bone, and skin are the most common sites of distant metastasis. A caveat is that pulmonary paragangliomas and primary skin paragangliomas do exist, and in patients with inherited paragangliomas with multiple tumors, that does not qualify as metastasis. Although lymph node dissection is not advocated by some authors, to date, there is one case report to our knowledge, of a single 0.2-cm regional (paratracheal) lymph node metastasis. Surgical removal is the mainstay of management for resectable metastasis. For unresectable tumors, radioactive isotope treatment and chemotherapy may be helpful. In the future, novel, targeted therapeutic options that prevent transformed cells from dividing indefinitely or that enhance programmed cell death may prove efficacious. As pathologists, our role will be including paraganglioma in the differential diagnosis for primary and metastatic disease, a judicious use of immunohistochemical stains to support the diagnosis of paraganglioma/pheochromocytoma, recommending surveillance for additional/multicentric tumors or metastasis, and triaging patients for optimal genetic testing with immunohistochemical stains for the loss of SDHB and SDHA proteins. To optimize patient care and provide clear and uniform information to our clinicians, the newly proposed synoptic reporting for pheochromocytomas and extra-adrenal paragangliomas will be helpful in issuing standardized pathology reports. Finally, because these tumors are known to develop late metastasis and are associated with unpredictable behavior, long-term clinical follow-up is prudent.

**CONCLUSION**

Thyroid paraganglioma is an extremely rare tumor, which morphologically can mimic follicular neoplasms, medullary thyroid carcinoma, and metastatic tumors. A misdiagnosis could mean poorer prognosis and unnecessary aggressive therapy for the patient. Hence, familiarity with this tumor, including this entity in the differential diagnosis of tumors with neuroendocrine features, and using immunohistochemical stains are helpful in arriving at the correct diagnosis.

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**References**


