

Primary Melanotic Paraganglioma of Thyroid Gland: Report of a Rare Case With Clinicopathologic and Immunohistochemical Analysis and a Literature Review

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ABSTRACT

BACKGROUND: Pigmented paraganglioma is a special type of paraganglioma, and it is rare in the thyroid.

CASE PRESENTATION: We report a case of a 41-year-old woman who had complained of a mass in the thyroid gland. Histology revealed tumor cells arranged in a nest-like or organoid pattern, separated by delicate fibrovascular septa. Two distinct components were observed. In the first, which constituted the majority of the tumor cells, no pigments were observed. In the second, a few cells with pigment showed intercellular substance, but the structure was unclear. Using immunohistochemistry, cells in the first component were confirmed to be diffuse strong positive for synaptophysin, but negative for chromogranin A, pan-cytokeratin, calcitonin, and thyroglobulin. About 1% of tumor cells were stained by Ki-67. In the margins of the tumor, a few cells were observed to be positive for HMB-45 and Melan A after bleaching by oxalic acid. The stromal cells were positive for S-100. Using electron microscopy, a few cells containing many round melanin bodies with greater electron density granules of nonuniform size were observed. The diagnosis of primary melanotic paraganglioma of the thyroid gland was made.

CONCLUSION: Primary melanotic paraganglioma of the thyroid gland is a rare, low malignant potential tumor. To the best of our knowledge, this is the first case described.

KEYWORDS: primary melanotic paraganglioma of thyroid gland, thyroid gland, paraganglioma

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Background

Paraganglioma seldom occurs in the thyroid. A comprehensive search of PubMed showed that only 38 cases had been reported in the English literature since 1974.^{1–27} However, no case contained melanin. Pigmentary paraganglioma is a special type of paraganglioma that usually occurs in the uterus,²⁸ orbit,²⁹ heart,³⁰ urinary bladder,³¹ and temporal horn,³² with reported cases also in the mediastinum, lumbar spine, retroperitoneum, and others.^{19,26} After reviewing, we found no reported cases in the thyroid. Here, we report this special presentation of thyroid paraganglioma with melanin, which was confirmed by immunohistochemistry and electron microscopy.

Case Presentation

A 41-year-old woman was hospitalized for a left thyroid mass, which had been found using type B ultrasonography. There was no enlargement of the lymph nodes in the neck on physical examination, and the color of the skin surface was normal. The mass was located in the left lobe of the thyroid, with an irregular shape, which indicated a malignant tumor. The maximum

diameter of the mass was 2.4 cm, detected by ultrasonic examination. Scattered clusters of atypical cohesive epithelioid cells were found in the mass of the thyroid by fine-needle aspiration. The hematoxylin-eosin staining of the specimen, together with frozen section and extensive immunohistochemistry, confirmed a diagnosis of paraganglioma of the thyroid gland with melanocytic differential. The patient underwent a mass excision, and no lesion was found using computed tomography or magnetic resonance imaging. Four lymph nodes, which showed no metastatic carcinoma (0 of 4), were isolated from the left neck.

The mass specimen was measured to be 3.5 cm × 2.3 cm × 2.0 cm. On the cut surface, all the visible area of the tumor was solid without cyst changes, with grayish white or black color, and the margins of the tumor were slightly irregular. Two distinct components were found in the black area of the tumor through microscopic observation. The first component, the majority of the mass, was composed of solid sheets and clusters of cohesive epithelial cells, with no pigment observed in the cytoplasm (Figure 1A, B). The second component comprised



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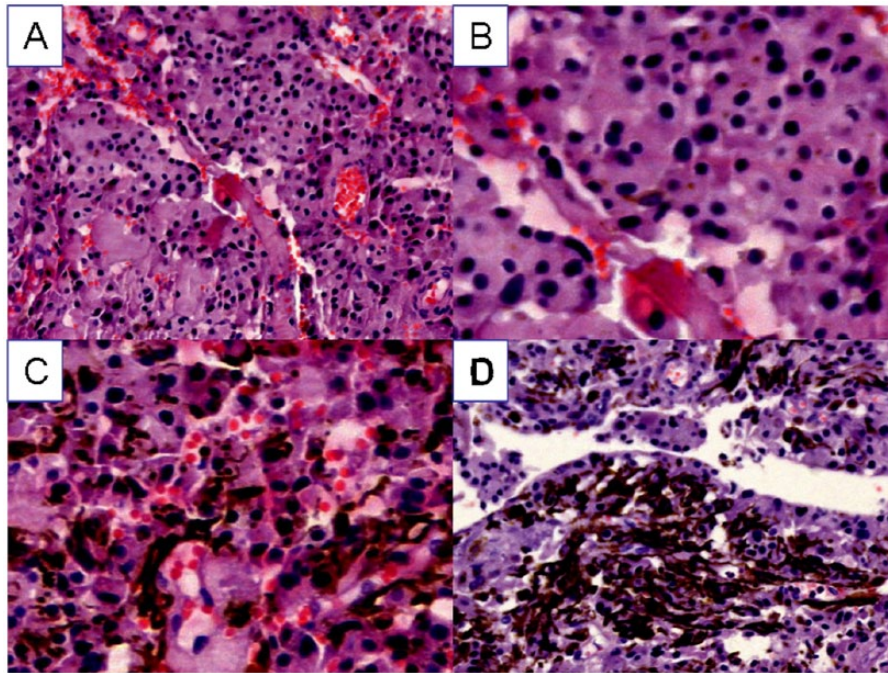


Figure 1. (A), (B) Tumor cells without pigment. (C), (D) Tumor cells with pigment in the cytoplasm.

cells covered by pigment, with the intercellular substance and structure unclear (Figure 1C, D). The tumor cells in the first component were arranged in a nest-like distribution without any gland cavity. The tumor consisted of monotonous sheets of cells with fluent and light-dyed cytoplasm, but without significant atypia. Tumor cells were round or polygonal, and the cytoplasm was basophilic. No mitotic figure was observed. There was no tumor thrombus observed in the vascular tissue after multiple dissections. Using immunohistochemistry, the tumor cells in the first component tested diffuse strong positive for synaptophysin (Syn) (Figure 2), but negative for chromogranin A (CgA), pan-cytokeratin, calcitonin and thyroglobulin. Ki-67 was positive in approximately 1% of tumor cells. A large quantity of pigments were within the stroma (Figure 1C). These pigments were negative for periodic acid-Schiff (PAS) and Prussian blue, but positive for Fontana-Masson. Of the cells surrounding the tumor, few were positive for HMB-45 and Melan A after bleaching by oxalic acid (Figure 3A, B). The stromal cells were positive for S-100 (Figure 3C). The tumor cells were negative for calcitonin and thyroglobulin (Figure 3D, E). The remaining tissue was free of tumor infiltration or metastasis.

Electron microscopy showed that the tumor was composed predominantly of polyhedral cells that had the features of paraganglion chief cells, although they exhibited greater nuclear pleomorphism than normal chief cells. Half of the chief cells had abundant cytoplasm with dispersed organelles and secretory granules (Figure 4); the other half had less cytoplasm and more closely approximated organelles and granules. Nucleoli, which were inconspicuous using light microscopy, were not

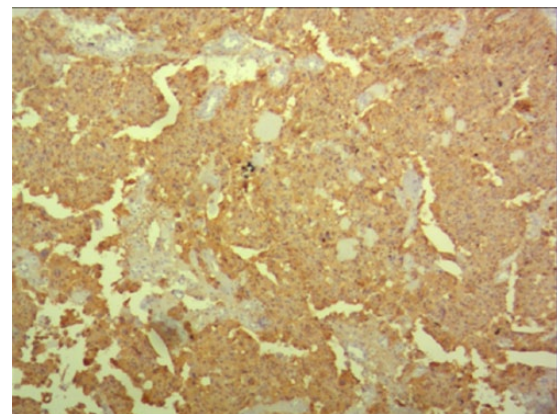


Figure 2. Synaptophysin diffusely expressed in the tumor cells.

prominent. The cytoplasm contained numerous mitochondria and many dense granules of the neurosecretory of endocrine type (Figure 4). These granules were of uniform electron density, membrane-limited, and 100 to 150 μm in diameter. Most had halos or clear spaces between the granules and the surrounding limiting membrane. Although the cytoplasmic margins of adjacent cells were difficult to evaluate, they appeared to interdigitate with one another. As is typical of paragangliomas, the tumor cells were closely related to the capillaries present within the stroma. The stroma itself appeared to be composed of fibrocytes and collagen with occasional histiocytes. Amyloid was not identified. Cells with ultrastructural features of sustentacular cells were extremely rare. A few had less cytoplasm and fewer organelles, and these also had many round melanin

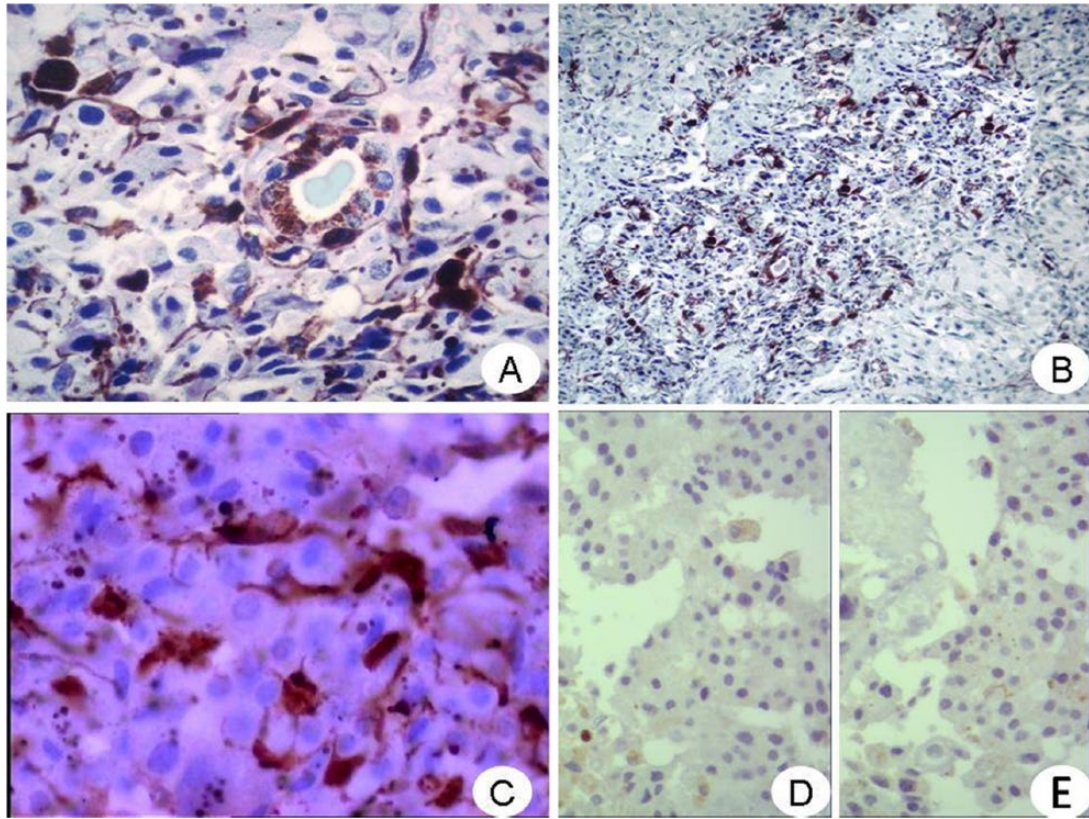


Figure 3. (A), (B) Few cells were positive for HMB-45 and Melan A after the tissue was bleached by oxalic acid. (C) The stromal cells were positive for S-100 after the tissue was bleached by oxalic acid. (D) The tumor cells were negative for calcitonin. (E) The tumor cells were negative for thyroglobulin.

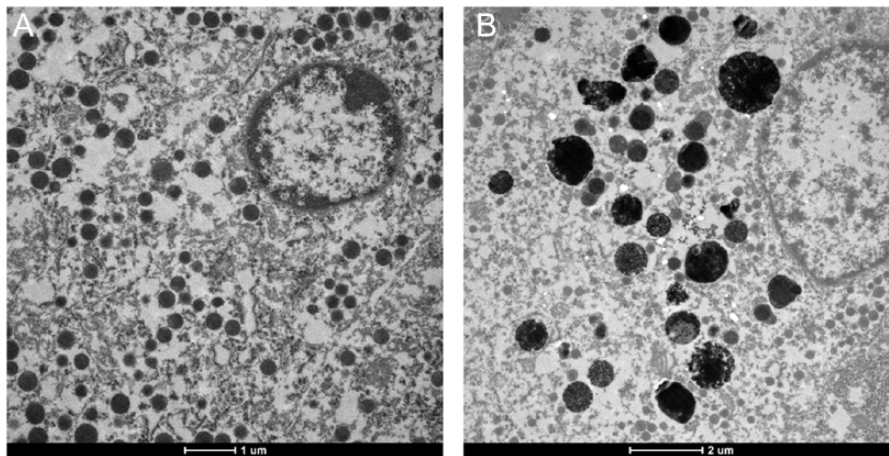


Figure 4. (A) Electron micrograph showing granules of uniform electron density, membrane-limited, and 100 to 150 μm in diameter; most had halos or clear spaces between the granule and the surrounding limiting membrane. (B) Many round melanin bodies with greater electron density granules of uniform size were observed.

bodies with greater electron density granules of nonuniform size (Figure 4).

The pathologic diagnosis was of primary pigmented paraganglioma of the thyroid gland without focal necrosis and vessel tumor thrombus. No recurrence or distant metastasis was observed after 19 months of follow-up.

Paraganglioma usually occurs in the area where paraganglia are distributed, such as the posterior peritoneum and the head and neck region.³³ Paraganglioma of the head and neck region mainly occurs in the carotid body, jugulotympanic, vagus nerve body, and auris media. However, paraganglioma is rarely found in the thyroid. Previous articles have reported that no

paraganglioma occurred in the thyroid and the precise pathogenesis of thyroid paraganglioma is unknown. We postulate that ectopic carotid body or jugulotympanic paraganglia could be a plausible origin of the lesion. Another possibility is that paraganglioma may originate from entrapped neuroendocrine progenitor cells of the dispersed neuroendocrine system, resulting from aberrant migration of the neural crest during embryogenesis.

Pigmental paraganglioma is a special and rare type of paraganglioma. Less than 38 cases have been reported since Tavassoli first reported two pigmental paraganglioma of the uterus. It featured multiple pigment particles in the cytoplasm. Pigmented paraganglioma has been reported across a wide age range (17-57 years), and no gender differences were noted. It has arisen in the bladder, posterior peritoneum, mediastinum, spine, and other sites. There is no functional symptom apparent, such as hypertension.

An unusual feature of this case was the presence of significant amounts of pigment. Based on histochemical staining or electron microscopy, the pigment has been classified as neuromelanin, lipofuscin, or true melanin. Herein, we present a case of thyroid paraganglioma with extensive melanin melanosis in the stroma. Using electron microscopy, the melanin globules were found in the chief cells. It was an interesting and unique case of paraganglioma with melanocytic differentiation without evidence of melanoma of the skin. Remarkable melanosis deposition was observed not only macroscopically but also microscopically. These pigments are negative for PAS and Prussian blue, but positive for Fontana-Masson. Electron microscopy showed that the tumor cells had large, pleomorphic granules with varying electron density, size, and shape, which are identified as neuromelanin. To the best of our knowledge, this is the first such case reported. Although primary melanoma of the thyroid gland has not been previously reported, paraganglioma with melanocytic differentiation was confirmed by morphologic and immunohistochemical staining, and melanoma was definitely excluded.

The diagnosis of paraganglioma mainly depends on the combination of morphology and immunohistochemistry. However, in previous reports, it was made by morphology, special staining, and electron microscopy, which could not distinguish paraganglioma and medullary carcinoma.³⁴ Because the head and neck paraganglioma is a nonfunctional tumor, there is no obvious clinical presentation other than a cervical lump. Thyroid paraganglioma, medullary thyroid carcinoma, and hyalinizing trabecular tumor (HTT) are difficult to distinguish only by histological morphology,^{34,35} so they are usually misdiagnosed before immunohistochemistry. As a result, all thyroid paragangliomas were identified as medullary thyroid carcinoma. Meanwhile, some paragangliomas are extremely similar to medullary carcinoma, the histological type of which is called "paraganglioma-like medullary carcinoma." It features high levels of serum calcitonin and more or less amyloid in tumor stroma.

Immunohistochemistry shows that apart from neuroendocrine markers such as neuron-specific enolase, CgA, and Syn, the tumor also expresses calcitonin, carcinoembryonic antigen, and cytokeratins. Even S-100-positive cells occurred in medullary carcinoma around the tumor nest, which has similar presentation with paraganglioma. However, it is difficult to confuse paraganglioma-like medullary carcinoma and paraganglioma. Comparatively speaking, HTT seldom occurs in the thyroid. The tumor cells are arranged as funicular or acini, resembling paraganglioma, and rare thyroid collagens are observed. Nevertheless, immunohistochemistry shows tumor cells are positive for thyroglobulin and thyroid transcription factor-1, and may express cytokeratins, but are negative for calcitonin. All these illustrate that the tumor cells originate from thyroid follicular epithelium. Genetic features suggest HTT is closely related to thyroid papillary carcinoma and may be the early period or histological type of papillary carcinoma, so immunohistochemistry can differentiate HTT from paraganglioma.

Of greatest concern to clinical doctors is whether paraganglioma is malignant or not because it relates closely to resection range and continuous therapy. However, with neuroendocrine tumors, benign and malignant are hard to differentiate for the pathologist. The prognosis of paraganglioma needs to be comprehensively assessed by surgical approach (biopsy, local resection, or complete resection), tumor size, operative margin, cell atypia, count of mitotic figure, necrosis, lymph node metastasis, vascular invasion, etc. Paraganglioma in the thyroid has been depicted as a benign progression in previous reports, although one reported that thyroid paraganglioma was malignant because it invaded the thyroid cartilage and penetrated through trachea wall into the tracheal mucosa. Its infiltrative growth mode seemed malignant, but others suspected it originated from cervical soft tissue rather than the thyroid.

Conclusions

Primary melanotic paraganglioma of the thyroid gland is a rare low malignant potential tumor in the thyroid. The tumor presented focal necrosis and high mitotic index, and intravascular tumor thrombus was observed. Although these presentations could not indicate definite malignancy for neuroendocrine tumors, frequent follow-up is essential for this type of tumor.

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Author Contributions

All authors made contributions to the acquisition, analysis, or interpretation of data. YD and ZW were involved in drafting the manuscript and revising it critically for important intellectual content. XZ gave final approval to the version to be published. All authors read and approved the final manuscript.

Availability of Data and Material

The data and material were available for review.

Consent for Publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Ethics Approval and Consent to Participate

The authors declare that the ethics approval and consent to participate were obtained for this study.

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