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CASE REPORT

Primary thyroid paraganglioma presenting with double thyroid nodule: a case report

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Abstract Paragangliomas (PGs) are exceptionally rare tumors. Only 24 cases have previously been reported. Both preoperative and postoperative differential diagnosis is very difficult. Due to interesting nature in diagnosis and differential diagnosis, we describe the case 58-year-old euthyroid woman with a thyroid PG. The patient had presented with euthyroid multinodular goiter to a secondary hospital. The patient was treated with right lobectomy, isthmectomy, and left partial lobectomy without any imaging procedures. No complication had been developed during and following the operation. Initial pathological examination suggested medullar thyroid carcinoma (MTC) in a nodule of 4.5 cm in diameter on right thyroid lobe and a nodule of 2.5 cm in diameter on the left thyroid lobe without amyloid stroma and referred to our third-stage hospital. Repeated pathological examination involving immunohistochemistry revealed that the tumor was stained positively to neuron-specific enolase, chromogranin A, synaptophysin, and S-100 protein. No immunoreactivity was detected against thyroglobulin, calcitonin, parathormone, carcino-embryonic antigen, thyroid transcription factor-1, and cytokeratin. A diagnosis of thyroid PG was finally made. Laboratory analyses and imaging procedures excluded any neck or extracervical tissues metastasis or multiple endocrine neoplasia. In conclusion, thyroid PG is an elusive tumor. We present this interesting nature thyroid PG case to highlight importance of careful evaluation of clinical and pathological findings to correctly identify paragangliomas which anatomically mimic MTCs. This report is the first case of thyroid PG presenting with multinodular goiter in the literature.

Keywords Thyroid gland · Paraganglioma · Neuroendocrine tumor

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Introduction

Paragangliomas (PGs) are uncommon neuroendocrine tumors which origins from the neural crest-derived paraganglia of the autonomic nervous system [1–5]. They are most frequently found in the head and neck, mainly associated with the carotid body, vagus nerve, jugulotympanic paraganglia, and, occasionally, the superior-inferior paraganglia [1, 4]. Thyroid PGs are thought to arise from the inferior laryngeal paraganglia which are sometimes situated within the thyroid capsule [5].

Thyroid PGs are exceptionally rare tumors which can be misinterpreted as medullary thyroid carcinomas (MTCs) [4]. To our knowledge, only 24 documented cases of thyroid PGs have been reported in the literature [1–3, 5–22].

In the present article, we report a case of a primary thyroid PG appearing as unusual double thyroid nodule which was first misdiagnosed as an MTC. This case is the first report from Turkey.

Case report

A 58 year-old female patient was referred to our Department from a secondary stage local hospital where she admitted to about 20 days ago due to gradually enlarged multinodular goiter for the last several months. Her history revealed that she had multinodular goiter during the last 3–4 years. By medical evaluation in the secondary stage hospital she had diagnosed to have grade 2 multinodular goiter. The diameters of thyroid nodules were 4.5 cm in the right lobe and 2.5 cm in the left lobe. Blood pressure and thyroid function tests results were within the normal limits. Her evaluation had not involve any imaging procedures (e.g., thyroid ultrasonography, thyroid scintigraphy, and cervical computerized tomography) or thyroid fine needle aspiration biopsy (FNAB), and she had underwent right lobectomy, isthmectomy, and left partial lobectomy. Her file history did not record any complications involving paroxysmal hypertension attacks and shock during and after the operation. Initial pathological examination had suggested a MTC in a nodule of 4.5 cm in diameter on the right thyroid lobe and in a 2.5 cm in diameter on the left thyroid lobe, without amyloid stroma. The patient was referred to our Department as the third stage-hospital for further evaluation (treatment). On physical examination, thyroid gland was nonpalpable. Cervical lymphadenopathy was not obtained. Thyroid function tests were consistent with postoperative hypothyroidism. Serum calcitonin level was low. Histopathological examination was repeated on the previously taken specimens and this re-evaluation revealed a benign thyroid paraganglioma in the two nodules. Light micrograph showed "Zellballen pattern" in thyroid nodules. There were nests of epithelioid cells (chief cells) with clear cytoplasm separated by a delicate fibrovascular stroma (Fig. 1). Mitotic activity was inconspicuous. Amyloid deposits were not detected at Congo red staining. No vascular invasion was found. On immunohistochemical staining, the tumor was strongly and entirely positive for neuron-specific enolase, chromogranin A, and synaptophysin (Fig. 2a). The sustentacular cells were positive for the S-100 protein (Fig. 2b). The tumor was negative for thyroglobulin, calcitonin (CT), parathormone (PTH), carcino-embryonic antigen (CEA), thyroid transcription factor-1 (TTF-1), and cytokeratin.

After the histopathological result was obtained, serum CT, CEA, PTH concentrations, and 24-h urinary catecholamines and their metabolites were measured and were within the normal ranges. Computed tomography scans of the head, cranium, thorax, and abdomen did not demonstrate any evidence of multiorgan tumor, local recurrence, distant metastases or concurrent tumor. ^{131}Iodine-metaiodobenzylguanidine (I-MIBG) scan was normal. In patient's family, there was no evidence of other family syndromes, e.g., multiple endocrine neoplasia (MEN) type 2, von Hippel-Lindau disease, neurofibromatosis type 1, and nonsydromic familial pheochromocytoma. Three months after surgical resections, the patient taking L-thyroxine 100 μg/day was asymptomatic. She was scheduled for further follow-up 3 month later for a neck ultrasound.

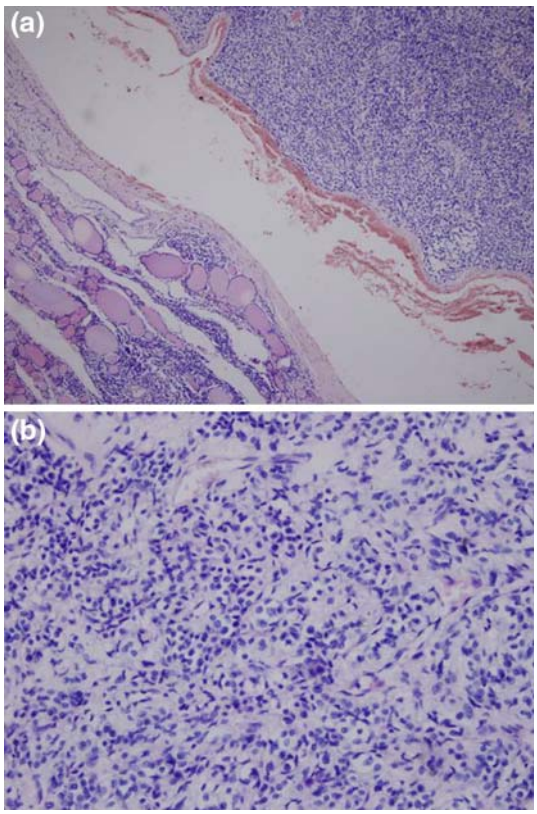

Fig. 1 Microscopic appearance of postoperative thyroid PG. **a** Neoplastic nodule adjacent to normal thyroid tissue (Hematoxylin and eosin, original magnification ×40), **b** The tumor cells are characteristically arranged in well-defined nests ("Zellballen") bound by a thin fibrovascular stroma. The cells have a finely granular cytoplasm. Most of the nuclei are usually round or oval with prominent nucleoli. (Hematoxylin and eosin, original magnification ×100)

Discussion

Intrathyroidal PGs are exceptionally rare tumors. To our knowledge, only 24 documented cases have been reported in the literature [1–3, 5–22]. Clinically, most of the cases were female; and between 40 and 60 years of age [1]. Usually, the thyroid PGs are asymptomatic and appears as nonfunctional solitary thyroid nodules for several years [1, 4, 5]. They can be easily confused clinically with more common intrathyroidal mass lesions [1, 2]. Unfortunately, imaging procedures and fine needle aspiration cytology have not been shown to be useful in differentiating the

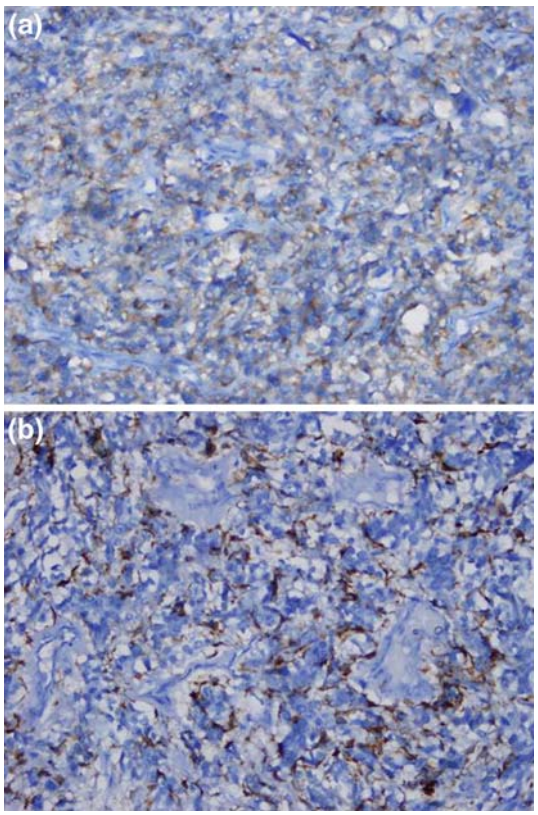

Fig. 2 **a** Tumor cells were positive for synaptophysin (immunoperoxidase staining, ×100), **b** Spindle-shaped sustentacular cells were positive for S-100 protein (immunoperoxidase staining, ×100)

diagnosis from thyroid carcinomas and other thyroidal mass lesions (e.g., hyalinizing trabecular adenoma, atypical follicular adenoma, and metastatic carcinoid tumors to the thyroid [1, 2, 16]. Because of the fact that thyroid PG is analogous to adrenal pheochromocytoma and other extra-adrenal paragangliomas [3, 23], it may potentially be functioning, as well.

In the present case, the correct diagnosis of thyroid PG could not be made preoperatively. Interestingly, PG was multinodular that manifested as two discrete nodules in both thyroid lobes. This report is the first case of thyroid PG presenting with multinodular goiter in the literature. But, PG was associated with other nonthyroidal disorders: in particular, MEN type 2 was excluded by normal levels of CT, catecholamine, and PTH values. In addition, in our case, unfortunately, imaging procedures and thyroid FNAB had not been performed before the surgery and they have not been measured urinary catecholamines and their metabolites. In the post-surgical period, to exclude the coexistence of pheochromocytoma, we measured the urinary catecholamines and their metabolites and found within the normal ranges. Also, our case was nonfunctioning thyroid PG.

The histopathological diagnosis of thyroid PG may be difficult. Differential diagnosis of this lesion should be made with laryngeal and carotid body PG arising adjacent to the thyroid, hyalinizing trabecular adenoma, PG-like, and poorly differentiated variants of MTC, metastatic carcinoma, and metastatic carcinoid tumor [4, 5]. In the present case, the surgeon did not observe any relationships between the tumor and carotid vessels and he dissected the tumor from the ipsilateral recurrent laryngeal nerve. Thus, carotid body or laryngeal PG invading the thyroid gland was excluded by above finding. Hyalinizing trabecular adenoma was excluded by the absence of intranuclear inclusions and nuclear grooves, and by negative immunostaining to TTF-1, thyroglobulin, and cytokeratin. Most problematic of all, thyroid PG resembles MTC. Both tumors are characterized by a prominent nesting pattern, immunohistochemical staining for neuroendocrine markers, and the ultrastructural presence of neurosecretory granules [2]. The diagnosis of thyroid PG is rarely diagnosed preoperatively or intraoperatively. Even after the review of the permanent section, thyroid PG is generally mistaken as MTC. In approximately 28% of the reported cases of thyroid PG including our own, an initial diagnosis of MTC was overturned after reevaluation of the thyroid tumor by another pathologist [2, 16]. In addition, clusters of tumor cells in MTC sometimes aggregate as zellballen. This variant is also named PG-like MTC [24]. To differentiate thyroid PG from MTC, a battery of immunohistochemical stains including markers of epithelial, neural, and hormonal differentiation are recommended [25]. However, negative staining to CT and CEA could not excluded the diagnosis of MTC, since rare cases of CT-negative MTC have been reported [15]. In the present case, S-100 protein-positive sustentacular cells were found: this finding is peculiar feature of PG. However, this finding is not a specific marker of PG, since a case of MTC with S-100 protein-positive sustentacular-like cells was reported [26]. In addition, in our case, amyloid deposits were not detected at Congo red staining.

PGs are often benign lesions, but the malignant PGs has also been reported in the literature [27]. The differential diagnosis between benign and malignant PG is very difficult histologically. Malignant PGs tend to show foci at necrosis, vascular invasion, and abundant mitotic figures [3, 27]. However, several authors suggest that there are no histological differences between the benign and malignant PGs, the only diagnostic criterion in favor of malignancy being the presence of local recurrence or distant metastases [2, 3, 28, 29]. In the present case, we did not observe infiltration of surgical resection margins and invasion of perithyroid tissues beyond the thyroid capsule, any metastases, vascular invasion, and necrosis. We considered the thyroid PG of our patient as a benign neoplasm.

However, a careful follow-up patient by neck ultrasound was recommended.

Total thyroidectomy or even thyroid lobectomy alone with long-term follow-up are the preferred treatment options and generally can be considered to be curative [1]. Elective neck dissection is not indicated in the treatment of thyroid PGs.

In conclusion, thyroid PG is an elusive tumor. Clinically, it is often dismissed silent thyroid nodule or nodules, whereas histopathologically it is easily mistaken for a highly malignant tumor, particularly MTC. Thyroid PG should be distinguished from other anatomically/histopathologically mimicking tumors in the thyroid.

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