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CASE REPORT

Thyroid paraganglioma – a rare entity

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Background

Thyroid paragangliomas (TPG) are rare neuroendocrine tumours that can create a diagnostic dilemma. Cytology and histopathology characteristics overlap with primary thyroid neoplasms, especially medullary thyroid carcinoma.[1] Over the last 50 years there have been 76 reported cases, making this one of the rarest thyroid neoplasms (< 0.01%). The first documented case of a TPG was in 1964 by Van Miert.[2]

Case report

A 50-year-old woman presented with a slow-growing, non-tender swelling in the neck. There was a history of hypothyroidism (Hashimoto's thyroiditis) for more than 10 years for which she was taking levothyroxine 100 mcg daily. She reported a history of hot flushes over the last few years, with no history of hormone replacement therapy. There were no adrenergic symptoms such as headache, sweating, palpitations or anxiety and no history of hypertension. There was no other significant medical, surgical and family history.

Clinical examination revealed a prominent left thyroid nodule, which was firm, non-tender and mobile on palpation. No cervical lymphadenopathy was palpable. On systemic examination a normal blood pressure and pulse rate were noted, with no features of hypertensive target organ damage or heart failure. No features of multiple endocrine neoplasia (MEN), Von Hippel–Lindau syndrome (VHL) and neurofibromatosis were noted.

On laboratory investigations, thyroid function tests, serum calcitonin (< 0.2 ng/l [0–5]) and CEA (< 1 ng/ml [0–5]) were normal. Plasma normetanephrines analysis showed a twofold increase (plasma normetanephrines = 414 pg/ml [0–196]) with normal plasma metanephrines. Urinary fractionated metanephrines and chromogranin A were not performed. Renal function and liver function were normal. Blood tests were consistent with Hashimoto's thyroiditis and menopause. Thyroid ultrasonography revealed a large (> 4 cm) solid hypoechoic left thyroid nodule (Figure 1) with increased peripheral and intranodal vascularity (Figure 1). The nodule had American Thyroid Association (ATA) sonographic features that were consistent with an intermediate suspicion pattern nodule (ACR-TIRADS = 4 [5 points]). Genetic testing for susceptibility genes was not available. Ethics approval was granted by the University of the Witwatersrand Human Research Ethics Committee (Ethics approval number: M200144).

An ultrasound guided fine-needle aspiration (FNA) was performed. The cytology smears were cellular, showing several groups of malignant cells. Immunochemistry (CD56 and calcitonin) was attempted directly on the slides, but both tests were negative. Morphologically, a medullary carcinoma was favoured, but not proven.

A total thyroidectomy was performed. Due to the proximity and association with the recurrent laryngeal nerve, the nerve was severed during the procedure. The patient also developed a haematoma in the neck on day 2 following the procedure. She was taken back to theatre for evacuation of the haematoma, washout of the operative bed and a cable nerve graft repair using the sural nerve was performed.

Histopathology of the thyroid gland showed a (50 × 30 × 25 mm) encapsulated solid tan-yellow nodule in the left lobe of the thyroid. There were background features of an auto-immune thyroiditis on microscopy. The nodule showed a nested ('zellballen') arrangement of epithelioid cells displaying focal severe nuclear pleomorphism with slender vascularised septae and prominent intervening vascularity (Figure 2). The cells showed prominent nuclear pleomorphism and pseudo inclusions with granular eosinophilic cytoplasm. No infiltration of the capsule or lymphovascular invasion was noted.

Immunohistochemistry results are displayed in Table 1 and Figure 3. The specimen was positive for synaptophysin, chromogranin A and S100 identified sustentacular cells. Cytokeratins, TTF1, CEA, thyroglobulin and calcitonin were negative.

During postoperative follow-up (±2.5 years) urinary fractionated metanephrines, chromogranin A and a whole-body PET/CT were normal. There was no evidence of local tumour recurrence, functional, multifocal or metastatic disease.

Discussion

Neuroendocrine tumours of the thyroid are rare and include medullary thyroid carcinoma, C-cell hyperplasia, mixed C-cell and follicular derived tumours, paraganglioma, intrathyroidal parathyroid adenoma and secondary metastases.[1] Most thyroid neoplasms arise from thyroid follicular cells, with papillary thyroid carcinoma being the commonest histologic subtype. The approximate incidence of extra-adrenal paragangliomas (PG) is 1 per 1 million persons.[3] PGs of the head and neck region arise from the parasympathetic nervous system and are usually non-functional (±1–3% are secretory) and are rarely malignant (±4–16%).[4] Parasympathetic PGs are usually only found in the head and neck area.[5,6] The most prevalent head and neck PG is a carotid body tumour, followed by glomus tympanicum and vagal paraganglioma.[7] Rare sites include the orbits, para-nasal sinuses, larynx, thyroid and parathyroid glands. The thyroid gland is one of the rarest locations for an extra-adrenal PG.[8]

TPGs are commoner in females (male: female ratio = 1: 8) and the mean age of presentation is 49.4 years. They usually present as a solitary incidentally detected thyroid nodule with

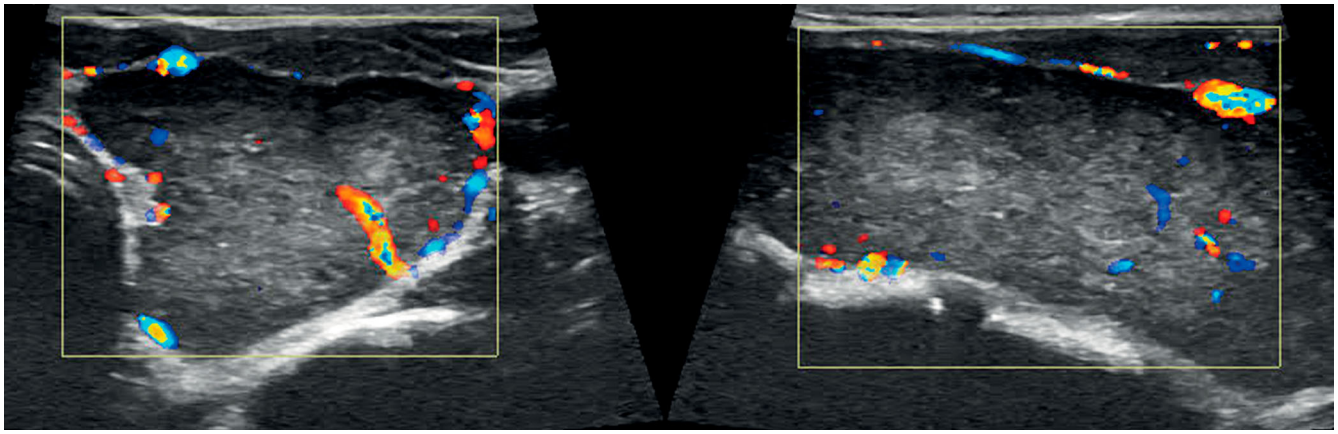

Figure 1: Solid hypoechoic thyroid nodule with increased peripheral and intranodal vascularity on ultrasound. ATA high suspicion sonographic pattern (ACR-TIRADS = 4 [5 points]).

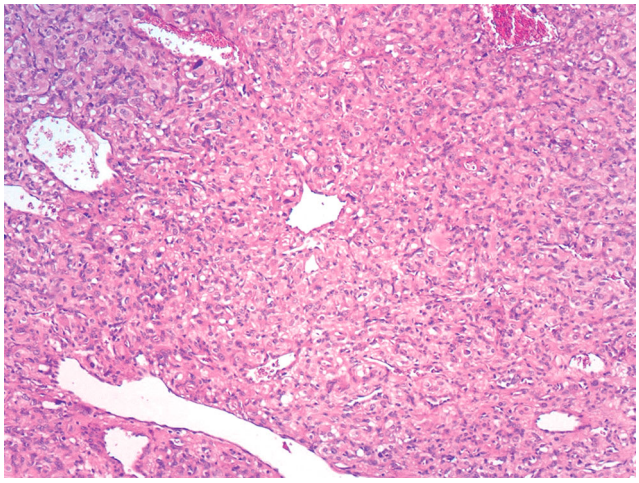

Figure 2: Zellballen arrangement of epithelioid cells with prominent intervening vascularity.

Table 1: Immunohistochemistry of the thyroid nodule

Immunohistochemistry	Result
Thyroglobulin	Negative
Chromogranin A	Positive
Synaptophysin	Positive
Calcitonin	Negative
CEA	Negative
S100	Positive
AE1/AE3	Negative
TTF1	Negative
Cam5.2	Negative

an average size of 3.5 centimetres. Patients often present with no compressive or adrenergic symptoms as TPGs are usually hormonally inactive. In this case, the elevated plasma metanephrines were likely a false-positive result as repeat testing was normal. TPGs are more frequently located in the right lobe and are associated with unilateral or bilateral carotid body tumours in 9.2% of cases.[7] Tumours are usually confined to the thyroid gland but may show infiltration into surrounding cervical tissues.[9,10]

Thyroid ultrasonography generally shows a solid, hypoechoic nodule with increased peripheral and intranodal vascularity. Thyroid scintigraphy, which is rarely used nowadays in the evaluation of a non-functioning thyroid, often displays a 'cold' nodule. Contrast-enhanced CT and MRI scan characteristics are similar to imaging of carotid body PGs.[11] Neuroendocrine tumours share a morphological kinship: they are often pleomorphic with tumour giant cells and spindle cells, and a medullary tumour would be considered the usual neuroendocrine tumour of the thyroid. As a result, TPGs are rarely diagnosed preoperatively with FNA or intraoperative frozen section histology.[7,11]

TPG cells originate from primitive neural crest cells. It is postulated that TPGs arise from the inferior laryngeal ganglion that has either been drawn inferiorly by the recurrent laryngeal nerve to lie adjacent to the thyroid or develops within the thyroid capsule. Common embryology between TPGs and primary thyroid tumours can explain similar cytological features.[7] The majority of PGs are sporadic; however, around 30–40% are associated with susceptibility genes (e.g. MEN1, NF1, RET, VHL, SDHA, SDHB, SDHC, SDHD, SDHAF2, TMEM127, EGLN1, EGLN2, HIF2A, KIF1B, FH and MAX). Approximately 30% of head and neck PGs are hereditary and are associated with tumour syndromes such as multiple endocrine neoplasia (MEN), VHL disease, neurofibromatosis and familial paraganglioma syndromes.[12,13]

Hemithyroidectomy or total thyroidectomy is the initial treatment of choice, with no reports of local recurrence documented postoperatively. Intraoperative findings that are consistent with a PG include a hypervascular thyroid nodule with a trabecular pattern of prominent veins, densely adherent to surrounding tissues, and substantial intraoperative bleeding. Elective lymph node dissection is usually not indicated. Careful and meticulous dissection to avoid trauma to the recurrent laryngeal nerve is advised. The role of radiotherapy is unknown and would not be used as first-line therapy due to the diagnostic dilemma posed by these lesions.

Follow-up of patients should include hormonal evaluation, imaging for multifocal or metastatic disease and genetic counselling. Due to the rarity of these tumours their clinical behaviour and natural history is not known. Unfortunately, there are no unequivocal histologic or immunohistochemical markers that distinguish benign from malignant paragangliomas. A PG

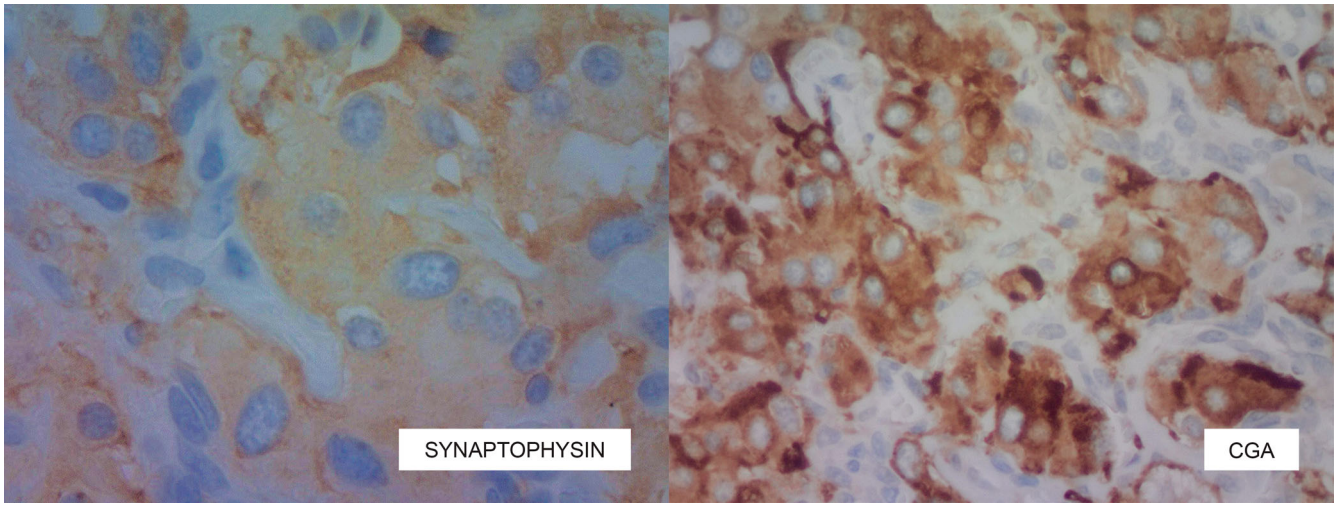

Figure 3: Positive immunohistochemistry for synaptophysin and Chromogranin A.

is deemed malignant if it metastasises to non-neuroendocrine tissues. Thyroid PGs have not been associated with distant metastases with follow-up of up to eight years in case series.[14]

Conclusion

TPG is a rare neuroendocrine tumour that can present as a primary thyroid malignancy. TPG should be considered in the evaluation of a thyroid nodule that has increased vascularity, and an FNA that suggests medullary thyroid carcinoma and normal serum calcitonin levels.

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