# PRIMARY PARAGANGLIOMA OF THE THYROID GLAND: CLINICAL AND IMMUNOHISTOLOGICAL ANALYSIS WITH A LITERATURE REVIEW

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## ABSTRACT

Primary paraganglioma of the thyroid is a rare neuroendocrine tumour, often mistaken for other thyroid neoplasms. Here, we describe a case of initially misdiagnosed primary paraganglioma of the thyroid and study its clinical presentation, management, investigation, and immunohistological findings.

A 72-year-old male presented with a left-sided solitary thyroid lobe and isthmus nodule. Ultrasound, fine needle aspiration, and computed tomography did not provide a clear diagnosis and subsequently, a left lobectomy and isthmusectomy were performed. The initial histopathological findings of the tumour revealed positivity to chromogranin and calcitonin, suggesting a medullary carcinoma replacing the left lobe of the thyroid. In a second histopathological review at an external laboratory, the tumour cells showed positive focal staining for chromogranin, but were negative for both calcitonin and monoclonal carcinoembryonic antigen, suggesting thyroid paraganglioma. This case highlights the importance of accurate histopathological diagnosis and the need to be aware of the possibility of thyroid paraganglioma initially presenting as a thyroid nodule.

Keywords: Primary paraganglioma, thyroid gland, clinical immunohistological analysis, medullary carcinoma, hyalinising adenoma.

## INTRODUCTION

Paragangliomas are neuroendocrine tumours that originate from the neural crest paraganglia of the autonomic nervous system.[1] The tumours can develop in a multitude of sites, including the head, neck, thorax, and abdomen. Within the head and neck region, the growths can present in the carotid, jugulotympanic, laryngeal, vagal, and orbital bodies. However, the thyroid gland represents an uncommon site for paraganglioma cells, with primary paraganglioma of the thyroid accounting for <0.1% of thyroid neoplasms.[2] In many cases, these tumours are endocrinologically silent.[3]

Due to the rarity of these tumours, they are often misdiagnosed, which could result in inappropriate management and treatment. Thus, proper diagnosis both clinically and histologically is of great importance. We will describe a case of misdiagnosed primary paraganglioma of the thyroid, which was initially thought to be a medullary carcinoma. In this article we will discuss the initial presentation of the case, its management, and how the final diagnosis was suggested histologically.

### Case Report

A 72-year-old male presented to the hospital with dyspnoea and hoarseness of voice caused by a left-sided solitary thyroid lobe and isthmus nodule. Physical examination of the patient revealed a large, solid, firm, painless mass on the left thyroid lobe without any palpable cervical lymph nodes.

The right lobe was unremarkable. The patient's vitals were within normal range. Indirect laryngoscopy showed paralysis of the left vocal fold, though movement in the right vocal fold was normal. Serum thyroid-stimulating hormone, triiodothyronine (T3), free thyroxin (T4), calcitonin, thyroglobulin, cortisol, urine metanephrines, and adrenocorticotropic hormone were all within normal limits. There was, however, elevated C-reactive protein levels (78.3 mg/L [<5.6 mg/L]) and an elevated neutrophil count 84.2% (42.0–75.0%).

The patient's family history was free of thyroid disease. An aneurysm of the abdominal aorta measuring 5.1 cm in diameter was noted in his personal medical history. There was no hypertension, flushing, diarrhoea, or other symptoms related to catecholamine hypersecretion present.

Ultrasound revealed a 7x4.3 cm mass showing microcystic features internally and extending inferiorly until the upper mediastinum (T3 vertebral level). Oedema was seen in subcutaneous fat, which could be indicative of inflammation. In addition, small circular lymph nodes were seen; the largest of which measured 1.2 cm in diameter. Ultrasound guided fine needle aspiration (FNA) biopsy of the thyroid was performed. The cytology report revealed erythrocytes, rare leukocytes, single follicular cells, and small follicular type aggregates without cytological abnormalities, which showed some oxyphilic (stainable without acid dye) metaplastic forms and were suggestive of a follicular lesion. Following FNA, computed tomography (CT) of the cervical area revealed that the left nodule was causing pressure posteriorly, displacing the left common carotid artery and outwardly displacing the internal jugular vein (Figure 1). Diagnostics did not include genetic testing, or a fluorodeoxyglucose-positron emission tomography scan to look for other tumours. The case was reviewed in a multidisciplinary team setting where it was decided that treatment should proceed with surgical resection of the left lobe and isthmus.

Surgery proved very difficult, due to the presence of a firm neoplasm that spread outside the thyroid capsule and was firmly attached to the surrounding neck structures, in particular to the left recurrent laryngeal nerve, trachea, and oesophagus. No lymph node enlargement was present. Intra-operative neuromonitoring was used, but there was no signal response from stimulating the left laryngeal recurrent nerve or the left vagus nerve. There were no post-operative complications and the patient left hospital 4 days following surgery.

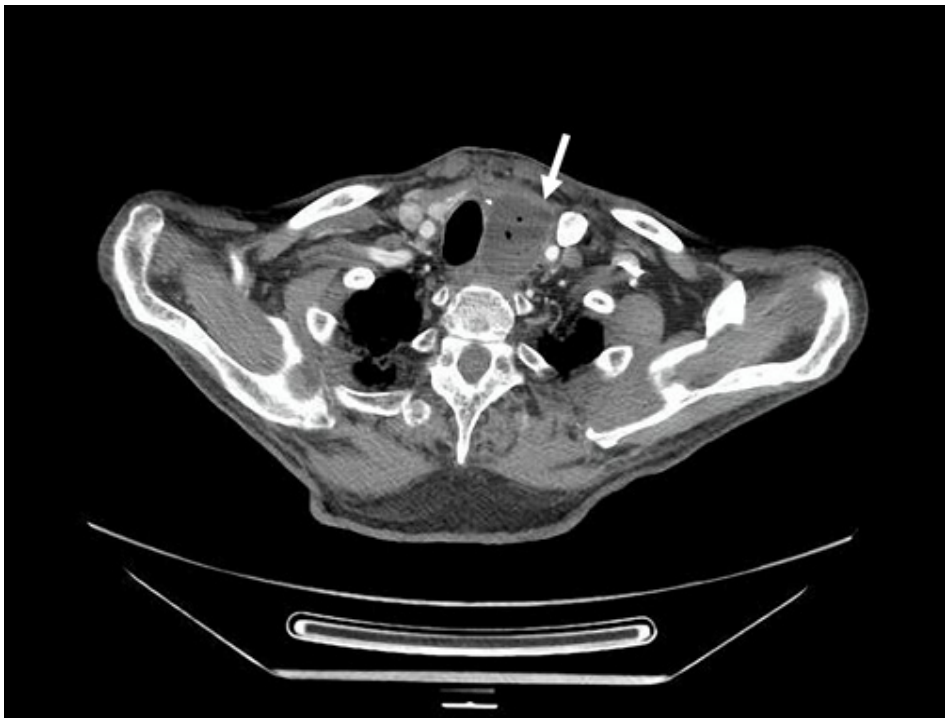

**Figure 1: Computed tomography of the cervical spine revealing the left nodule pushing and causing pressure, posteriorly displacing the left common carotid artery and outwardly displacing the internal jugular vein.**

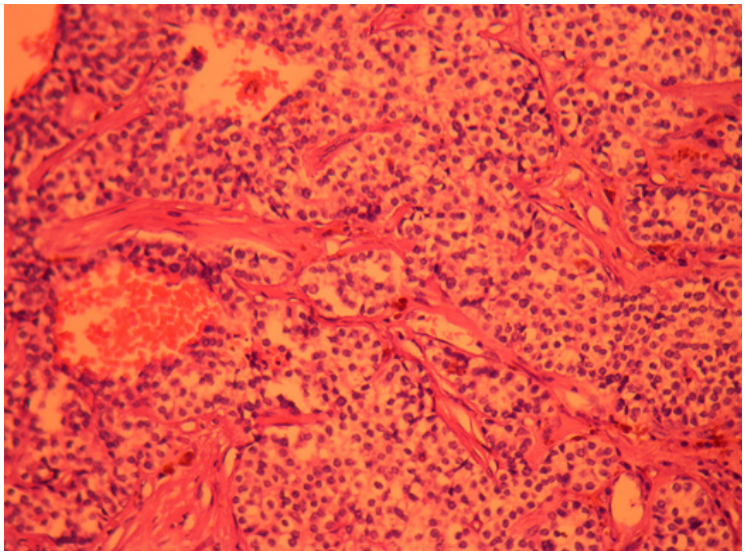

**Figure 2: Thyroid tissue infiltrated by a tumour that is composed of closely packed solid groups of polygonal neoplastic cells with eosinophilic cytoplasm and round-to-oval nuclei containing granular chromatin. The groups of cells are separated by abundant capillaries and dilated vessels.**

### Immunohistology

Conventional histology and immunochemistry were performed. On microscopic examination the left lobe was extensively infiltrated by a small-celled tumour. The tumour was composed of fused small malignant cells infiltrating the fibrous stroma and replacing the entire left lobe. No obvious amyloid was identified (Figure 2).

The immunomarkers used included synaptophysin, chromogranin A, calcitonin, thyroglobulin, thyroid transcription factor 1 (TTF1), cytokeratin (CK)-7, and CK20. The neoplastic cells were positive for chromogranin and calcitonin, which suggested a diagnosis of medullary carcinoma replacing the left lobe of thyroid. Due to the lack of experience within the local lab in identifying rare types of cancer histology, the slides were later sent to London, UK, for a re-assessment of the histopathology and immunochemistry. Upon re-examination, histology revealed thyroid tissue infiltrating with a tumour composed of closely packed solid groups of polygonal neoplastic cells with pale stained cytoplasm and rounded darkly stained nuclei. Immunology showed positive focal staining for chromogranin and negative for both calcitonin and monoclonal carcinoembryonic antigen (CEA). The conclusion was reached that although calcitonin-poor medullary carcinoma has been described, the additional absence of CEA suggested that thyroid paraganglioma should be considered a stronger possibility.

## Outcome and Follow-up

One year after diagnosis, the patient is alive and well without evidence of disease recurrence.

## DISCUSSION

Paraganglioma of the thyroid gland is an extremely rare neuroendocrine tumour[4] first described in 1964. To the best of our knowledge, between 1964 and 2013 a total of 39 cases were reported in the literature. Of the reported cases, only five patients were male (male:female, 1:6.8), with an age range of 9–73 years old at presentation (median, 50 years old; mean, 47.8 years old; Table 1). The location of the paragangliomas reported varies with respect to the thyroid gland as the tumour can arise at the isthmus, or in the left and/or right thyroid gland tissues. In most cases, paragangliomas are confined to the thyroid gland; however, some may be locally invasive to the tracheal wall,[5,6,7] larynx/pharynx,[7] cricoid cartilage,[1] subglottis,[8] or recurrent laryngeal nerve.[9]

Clinically, paraganglioma of the thyroid gland can mimic other more common thyroid pathologies and presents as a mass or nodule. As a result, the tumour may go unnoticed, or be dismissed as a goitre, thyroglossal cyst, or follicular adenoma for a significant amount of time. In some cases, the tumour can also present with additional pathologies such as papillary thyroid carcinoma, parathyroid adenoma, and bilateral carotid body

paragangliomas.[14] What makes the diagnosis more challenging is its immunohistology, which may be difficult and is often mistaken for medullary carcinoma or hyalinising adenoma of the thyroid. In our case, the paraganglioma was initially thought to be a medullary carcinoma. This confusion can arise due to medullary carcinoma exhibiting a nesting (paraganglioma-like) pattern of growth.

**Table 1: Primary paraganglioma of thyroid gland; review of 39 cases reported in literature.**

| Author | Sex | Age (Years) | Presenting symptom | Surgery and/or other treatment | Follow-up |
|---|---|---|---|---|---|
| Armstrong[5] | F | 67 | Mass | Left lobectomy, isthmusectomy, tracheal resection of rings 3–6 | Dead (colon adenocarcinoma) 8 years post surgery |
| | M | 64 | Mass, dyspnoea on exertion, progressing stridor | Total thyroidectomy, tracheal resection | Alive and well 14 years post surgery |
| | M | 60 | Right mass | Total thyroidectomy | - |
| Ashraf[10] | F | 40 | Right mass | Surgical resection | - |
| Banner[11] | F | 36 | Mass | Left lobectomy | - |
| Bizollon[12] | F | 48 | Cold nodule | - | - |
| Brownlee[8] | F | 27 | Mass | Right lobectomy, right subglottic laryngectomy | Alive and well 18 months post surgery |
| Buss[13] | F | 50 | Tender cold nodule | Left hemithyroidectomy | Alive and well 30 months post surgery |
| Cayot[14] | F | 58 | Enlarging goitre | Total thyroidectomy | - |
| Corrado[15] | F | 46 | Mass, hypertension | Right lobectomy, isthmusectomy | - |
| de Vries[16] | F | 73 | Mass, hoarseness, trachea compression | Left hemithyroidectomy | Alive and well 2 years post surgery |
| Erem[17] | F | 58 | Multinodular goitre, growth | Right lobectomy, isthmusectomy, partial left lobectomy | Alive and well 3 months post surgery |
| Ferri[9] | F | 63 | Mass, hypertension | Right lobectomy | Alive and well 18 months post surgery |
| Foppiani[18] | F | 51 | Hot nodule, hyperthyroidism | Total thyroidectomy | Alive and well 5 years post surgery |
| Gonzalez[19] | F | 36 | Mass | Total thyroidectomy | Alive and well 2 months post surgery |
| Haegert[2] | F | 36 | Tender cold nodule | Left hemithyroidectomy | Alive and well 5 years post surgery |
| Hughes[20] | F | 50 | Cold nodule | Total thyroidectomy | Alive and well 2 years post surgery |
| Kronz[21] | M | 55 | Hypertension, left lesion | Left lobectomy, isthmusectomy | Alive and well 9 months post surgery |
| | F | 52 | Enlarging neck mass, trachea compression | Total thyroidectomy, radiotherapy | Alive and well 6 years post surgery |
| La Guette[22] | F | 55 | Mass | Total thyroidectomy | Alive and well 4 years post surgery |
| | F | 64 | Cold nodule | Left hemithyroidectomy | Alive and well 7 years post surgery |
| | F | 56 | Mass | Right hemithyroidectomy | Alive and well 8 years post surgery |
| Massaioli[23] | F | 9 | Mass | Subtotal thyroidectomy | Alive and well 5 months post surgery |
| Mitsudo[6] | F | 50 | Mass, hypertension | Total thyroidectomy, segmental anterior resection of trachea | Alive and well 2 years post surgery |
| Mun[24] | F | 40 | Recurrent multinodular goitre | Total thyroidectomy | Alive and well |

**Table 1 continued.**

| Author | Sex | Age (Years) | Presenting symptom | Surgery and/or other treatment | Follow-up |
|---|---|---|---|---|---|
| Napolitano[25] | F | 47 | - | Total thyroidectomy | Alive and well 6 months post surgery |
| Olofsson[7] | F | 44 | Mass | Left lobectomy, partial pharyngectomy, total laryngectomy, partial tracheal resection | Alive and well 7 years post surgery |
| Phitayakorn[26] | F | 41 | Mass | Surgical resection | Alive and well 14 months post surgery |
| | F | 73 | Enlarging right hypervascular mass | Right hemithyroidectomy | Alive and well 13 months post surgery |
| Skiadas[27] | F | 54 | Mild tachycardia, hypertension, cold nodule | Total thyroidectomy | Alive and well 22 months post surgery |
| Tiong[28] | F | 52 | Mass | Left lobectomy | Alive and well 2 years post surgery |
| Van Miert[4] | F | 63 | Mass, hypertension | Radiotherapy | - |
| Vera-Cruz[29] | F | 32 | Mass | Right hemithyroidectomy | Alive and well 4 years post surgery |
| Vodovnik[30] | F | 46 | Palpable tender mass, hypertension | Right lobectomy | - |
| Yano[31] | M | 24 | Right hypervascular mass | Right lobectomy | Alive and well 6 months post surgery |
| Yu[32] | F | 30 | Mass | Left lobectomy, subtotal right lobectomy | Alive and well 39 months post surgery |
| | M | 47 | Right mass | Right lobectomy | Alive and well 47 months post surgery |
| | F | 37 | Mass | Right lobectomy, isthmusectomy, partial left lobectomy | Alive and well 10 months post surgery |
| Zantour[1] | F | 32 | Mass | Total thyroidectomy, resection of cricoid cartilage | Alive and well 6 years post surgery |

M: Male; F: Female.

The diagnosis of paraganglioma of the thyroid is difficult to confirm using only FNA, ultrasound, or CT. Diagnosis is usually confirmed post surgically with immunohistology of the resected mass. Immunohistology helps distinguish medullary carcinoma and hyalinising adenoma of the thyroid from paraganglioma of the thyroid. It is often difficult to distinguish between medullary carcinoma and paraganglioma of the thyroid gland, as both have clusters of cells with granular cytoplasm (chromogranin A, synaptophysin, and neuron-specific enolase positive) and a richly vascularised stroma. However, only paraganglioma of the thyroid gland exhibits S-100 staining and lacks CK, CEA, and calcitonin staining.[9] Conversely, some medullary carcinomas stain S-100.[15,22] As the clinical management and sequel strategy of each respectively vary, it is vital to differentiate between them. Medullary carcinomas originate in the parafollicular C cells of the thyroid and thus stain with calcitonin. Additionally, they contain amyloid material and thus can be stained with Congo red. Rarely, cases of medullary carcinoma may be negative for calcitonin,[15] and paraganglioma may be positive for calcitonin or CK,[21] which might make differentiating between the two tumours even more challenging.

Another neoplasm that can sometimes be confused as paraganglioma is hyalinising adenoma of the thyroid. Hyalinising adenoma is a thyroid tumour of follicular cell origin with a trabecular pattern consisting of cells arranged around delicate vessels. Hyalinising adenoma stains positive for

thyroglobulin and TTF1. However, like paraganglioma of the thyroid, it stains negative for calcitonin and it may stain positive for chromogranin A and neuron-specific enolase.[33] This may also make the diagnosis of paraganglioma more challenging.

The majority of reported patients are alive and well with no evidence of disease recurrence following resection of a paraganglioma of the thyroid gland. In most cases, surgical resection and long-term follow-up were the preferred management options. One case received supplemental radiotherapy,[21] and another radiotherapy alone.[4] Radiotherapy is recommended where there is a suspicion of residual tumour, or when surgery is not feasible.

In summary, preoperative examinations are not ideal for diagnosis of paraganglioma. With the correct immunohistological techniques, it is possible to confirm paraganglioma of the thyroid gland and to rule out other pathologies, despite the variability in immunohistological staining between different neoplasms. Paraganglioma of the thyroid gland appears to have a favourable outcome, despite its challenging diagnosis; surgery and long-term follow-up is the advised management plan.

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