**Abstract (150 words)**

Paraganglionoma of the thyroid is an extremely rare tumour, with fewer than thirty cases reported in the literature. These tumours are believed to arise from the inferior laryngeal paraganglia and are most common in females of middle age. Approximately 30% of head and neck paraganglionomas are hereditary, most frequently due to germline mutations in the succinate dehydrogenase gene family, but also in association with disorders including multiple endocrine neoplasia and von-Hippel Lindau disease. This entity is frequently mistaken for other lesions, including secondary neuroendocrine tumours and follicular neoplasm. Treatment is by total thyroidectomy, or lobectomy for a solitary lesion. Despite the presence of atypical features, malignant transformation of these tumours has not been observed, with no reported recurrences following resection.

**Main text (750 words)**

* **Case report**

A 50-year old male presented to his GP with a 2-week history of an asymptomatic left-sided neck mass. He had a past medical history of post-traumatic seizures, which were well-controlled with antiepileptics. There was no significant family history of any disease.

The mass was classified as malignant by both an ultrasound scan of the neck and fine needle aspiration cytology of the lesion. The patient therefore underwent total thyroidectomy. A frozen section from the left lobe during the procedure showed pleomorphic malignant cells. At histology, sections from the left thyroid lobe showed infiltration by cells with abundant granular cytoplasm. Although the mitotic rate was very low, significant nuclear pleomorphism was noted. In areas, the tumour showed a nested appearance, but also had an infiltrative, permeative pattern, with tumour cells present at the surgical margins. There was no definite vascular invasion or necrosis. Thick, sclerotic keloidal collagen was present in some areas of the stroma.

On immunohistochemistry, the tumour cells were strongly positive for neuroendocrine markers (synaptophysin and chromogranin), with S-100 positivity in sustentacular cells. Tumour cells were negative with stains for TTF-1, thyroglobulin, CEA, MNF-116 and calcitonin. The morphology and immunoprofile were those of a paraganglionoma.

* **Discussion and conclusion – in light of previous relevant literature**

Paraganglionomas are usually benign tumours of the autonomic nervous system, derived from the primitive neural crest1. Primary paraganglionomas of the thyroid are rare tumours, representing less than 0.1% of all thyroid neoplasms2. Fewer than thirty cases have been reported in the literature3. Lesions most frequently occur in middle-aged females, where they usually present as an asymptomatic mass of longstanding duration4: as a result of their origin from the parasympathetic nervous system, paraganglionomas of the thyroid usually show minimal secretion of catecholamines, or are non-secretory4. They are believed to originate from the inferior laryngeal paraganglia1 4, which may be situated within the thyroid capsule.

The differential diagnosis includes medullary carcinoma of the thyroid, particularly when the tumour displays a nested appearance. Thyroid paraganglionomas are not usually diagnosed pre-operatively by either ultrasonography or fine needle aspiration biopsy, or intra-operatively at frozen section2. These tumours are most frequently misdiagnosed as medullary carcinoma of the thyroid1: these entities may be distinguished by Congo red staining of the stromal amyloid, and tumour positivity for calcitonin, in medullary carcinoma2.

At resection, most are well-circumscribed, solitary lesions, with a tan-grey cut surface4. Histologically, thyroid paraganglionomas are similar to those seen at other sites, being composed of chief cells and sustentacular cells with a distinctive nested appearance2. In a 2013 review, 42% of cases to date described nuclear pleomorphism (as in this case), with 13% of cases showing moderate to severe nuclear atypia2. Mitotic figures and necrosis are generally rare. No histological features appear to be predictive of prognosis. Although most thyroid paraganglionomas are localised to the thyroid, these tumours may occasionally invade adjacent structures4. Additionally, approximately 14% of patients have associated disease in the carotid body or vagal paraganglia4, meaning that follow-up imaging after surgery is desirable. Despite the atypical features, none of the cases reported to date have shown aggressive behaviour or malignant transformation, even in cases with local invasion2.

Approximately 30% of head and neck paraganglionomas are hereditary, and may be associated with multiple endocrine neoplasia, von-Hippel Lindau disease, neurofibromatosis and familial paraganglionoma syndromes 1 to 44. The majority of inherited cases are attributable to germline mutations in succinate dehydrogenase B (*SDHB*), C (*SDHC*), D (*SDHD*), or succinate dehydrogenase assembly factor 2 (*SDHAF2*)2. There have been occasional reports of head and neck paraganglionomas associated with mutations in *VHL*, *TMEM127* and *SDHA4*. Mutations in *MEN1*, *NF1*, *RET*, *EGLN1*, *HIF2A*, *KIF1Bβ* and *MAX* also confer susceptibility to paraganglionomas. Only succinate dehydrogenase B mutations are known to be predictive of malignancy2. Here, the patient was referred for genetic testing. No known pathogenic mutations were detected in the *SDHB*, *SDHC*, *SDHD*, *SDHAF2*, *TMEM127* or *VHL* genes. Screening for further endocrine dysfunction was negative, and he remains recurrence-free over two years following his initial presentation.

* **Practice points – 3-5 important points as a bulleted list**
* Thyroid paraganglionomas are rare tumours, most frequently presenting as an asymptomatic neck mass in middle-aged women
* Medullary thyroid cancer should be included in the differential diagnoses: thyroid paraganglionomas are a potential diagnostic pitfall
* The preferred treatment is total thyroidectomy, or lobectomy for a solitary lesion
* Some mutations in *SDHB* are associated with an increased risk of metastasis
* Patients should undergo post-operative investigation for functional, multifocal or metastatic disease
* **References (6 maximum)**

1. Zantour B, Guilhaume B, Tissier F, et al. A thyroid nodule revealing a paraganglioma in a patient with a new germline mutation in the succinate dehydrogenase B gene. *European journal of endocrinology* 2004;151(4):433-8. [published Online First: 2004/10/13]

2. Yu B-H, Sheng W-Q, Wang J. Primary Paraganglioma of Thyroid Gland: A Clinicopathologic and Immunohistochemical Analysis of Three Cases with a Review of the Literature. *Head and Neck Pathology* 2013;7(4):373-80. doi: 10.1007/s12105-013-0467-7

3. Ferri E, Manconi R, Armato E, et al. Primary paraganglioma of thyroid gland: a clinicopathologic and immunohistochemical study with review of the literature. *Acta Otorhinolaryngologica Italica* 2009;29(2):97-102.

4. Lee SM, Policarpio-Nicolas ML. Thyroid Paraganglioma. *Archives of pathology & laboratory medicine* 2015;139(8):1062-7. doi: 10.5858/arpa.2013-0703-RS [published Online First: 2015/08/01]

* **Multiple choice questions – three single best answer**

1. Mutations in which gene are associated with an increased risk of malignancy in thyroid paraganglionoma?

a. *RET*

b. *VHL*

c. *SDHB*

d. *NF1*

2. Thyroid paraganglionomas can be distinguished from medullary thyroid carcinoma using which stain?

a. Calcitonin

b. Chromogranin

c. TTF-1

d. Thyroglobulin

3. What proportion of thyroid paraganglionomas are hereditary?

a. 20%

b. 30%

c. 50%

d. 75%

* **Figures – up to 6, 8 cm width**