The Management of Locally Invasive Primary Thyroid Paraganglioma: A Case Report and Review of the Literature

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Abstract Paragangliomas (PG) are very rare neuroendocrine tumours, arising from neural crest derived paraganglia of the autonomic nervous system. Primary thyroid paraganglioma (PTPG) is a rare site of PG and only 45 cases have been previously reported. The preoperative diagnosis of PTPGs presents a challenge as the clinical, cytological and histological features overlap with more common primary thyroid cancers. A 55 year old male was found to have significant enlargement of the left lobe of his thyroid. Following lobectomy, the thyroid lobe showed unencapsulated tumour which was positive for synaptophysin, CD56 and S100 (sustentacular cells). Post-operative imaging demonstrated incomplete resection. There was no post-operative radiotherapy and monitoring was by 6–12 monthly MRI. 48 months after his surgery he is alive and well with no evidence of disease progression. The diagnosis of PTPG was only made postoperatively, and although rare should be considered in the differential diagnosis of a hypervascular thyroid nodule.

Keyword Thyroid paraganglioma · CD56 · Synaptophysin

Introduction

Paragangliomas (PG) are very rare neuroendocrine tumours, arising from the neural crest-derived paraganglia of the autonomic nervous system. Prominent locations of head and neck PGs include the carotid body along with the vagal, jugular, and tympanic glomus [1], and account for 0.6 % of all head and neck tumours [2]. Less common sites of head and neck PGs include the nasal cavity, orbit, larynx and thyroid gland [3]. In a recently published article, primary thyroid paragangliomas (PTPGs) accounted for 0.04 % of the final histological diagnosis of patients undergoing thyroidectomy during the period 1981–2008 [4].

To the best of our knowledge, (from reviewing the world literature written in the English language), 45 cases of PTPGs have been reported between 1965 and 2016 (Table 1) [2, 4, 5, 7, 8, 10–39]. Only 5 of these cases occurred in men [4, 5, 7, 38], suggesting the predilection of this disease towards the female sex [4, 5].

The pre-operative diagnosis of PTPGs presents a challenge to the otolaryngologist and pathologist since the clinical, cytological and histological features overlap with more common primary thyroid cancers, namely medullary thyroid carcinoma (MTC). Although rare, PTPGs should be considered in the differential diagnosis of a hypervascular thyroid nodule [8]. In this case study, we report a 55 year old male with locally invasive PTPG, its clinical, radiological and immunohistochemical features and its management.

Case Report

A 55 year old military officer was found to have significant enlargement of the left lobe of his thyroid, which was picked up on a pre-discharge medical check-up. Although

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Table 1 Overview of historical cases of PTPGs

Author	Year	Sex	Age	Local invasion	Treatment	Resection	Multicentric disease	Follow up
Van Miert [10]	1964	F	63	NA	Radiotherapy	NA	Syn CBT	16 mnths
Kay et al. [11]	1975	F	51	No	Surgical resection	Complete	No	7.5 mnths
Massaioli et al. [12]	1979	F	9	NA	Subtotal thyroidectomy	Complete	No	5 mnths
Banner et al. [13]	1979	F	36	No	Hemithyroidectomy	NA	No	NA
Haegert et al. [14]	1980	F	36	No	Hemithyroidectomy	Complete	Bilat CBT	5 years
Buss et al. [15]	1980	F	50	No	Hemithyroidectomy	Complete	No	2.5 years
Cayot et al. [16]	1982	F	58	No	Total thyroidectomy	NA	Bilat CBT	7 mnths
Olofsson et al. [17]	1984	F	44	Yes	Hemithyroidectomy + partial pharyngeal + total laryngeal + partial tracheal resection	Complete	No	7 years
Mitsudo et al. [18]	1987	F	50	Yes	Total thyroidectomy + segmental anterior tracheal resection	Complete	No	2 years
de Vries and Watson [19]	1989	F	73	Yes	Hemithyroidectomy	Complete	No	2 years
Brownlee and Shockley [20]	1992	F	27	Yes	Hemithyroidectomy extended to right subglottic laryngeal resection	Complete	No	18 mnths
Hughes et al. [21]	1997	F	31	No	Hemithyroidectomy to completion total thyroidectomy	Complete	Met CBT	2 years
LaGuette et al. [22]	1997	F	56	No	Hemithyroidectomy	Complete	No	8 years
	1997	F	64	No	Hemithyroidectomy	Complete	No	4 years
	1997	F	55	No	Total thyroidectomy	Complete	No	7 years
Bizollon et al. [23]	1997	F	48	NA	Not available	NA	No	NA
Tiong et al. [24]	2000	F	52	No	Hemithyroidectomy to completion total thyroidectomy 4 weeks later	Complete	No	2 years
Kronz et al. [5]	2000	M	55	No	Hemithyroidectomy	Complete	No	9 mnths
	2000	F	52	Yes	(1) Hemithyroidectomy + tracheostomy (2) Post-op RT (3) Completion TT + total laryngeal, pharyngeal, oesophageal resection + central and bilateral neck dissection	Complete after 2nd surgery	No	6 years
Napolitano et al. [25]	2000	F	47	No	Total thyroidectomy	Complete	No	6 mnths
Skiadas et al. [26]	2001	F	65	No	Total thyroidectomy	Complete	No	22 mnths
Vera-Cruz et al. [27]	2001	F	32	NA	Hemithyroidectomy	NA	No	4 years
Vodovnik [28]	2002	F	46	No	Hemithyroidectomy	Complete	No	NA
Corrado et al. [29]	2004	F	46	Yes	Hemithyroidectomy	Incomplete	No	3 mnths
Zantour et al. [30]	2004	F	32	Yes	Total thyroidectomy	Complete	No	6 years
Foppiani [31]	2005	F	51	No	Total thyroidectomy	Complete	No	5 years
Yano et al. [7]	2007	M	24	No	Hemithyroidectomy	Complete	No	6 mnths
Ashraf et al. [32]	2008	F	40	NA	Surgical resection	NA	No	NA
Ferri et al. [2]	2009	F	63	Yes	(1) Hemithyroidectomy (2) RT planned for residual tumour	Incomplete	No	18 mnths

Table 1 continued

Author	Year	Sex	Age	Local invasion	Treatment	Resection	Multicentric disease	Follow up
Gonzalez Poggioli et al. [33]	2009	F	36	No	Total thyroidectomy	Complete	No	2 mnths
Erem et al. [34]	2009	F	58	No	Subtotal thyroidectomy	Complete	No	3 mnths
Mun et al. [35]	2009	F	40	No	Total thyroidectomy	Complete	No	NA
Phitayakorn et al. [8]	2011	F	41	No	Surgical resection	Complete	No	14 mnths
	2011	F	73	Yes	Hemithyroidectomy	Complete	No	13 mnths
Basu and Viswanathan [36]	2011	F	70	No	Hemithyroidectomy	Complete	No	12 mnths
Castelblanco et al. [37]	2011	F	59	No	Surgical resection	NA	No	NA
	2011	F	78	No	Surgical resection	NA	No	NA
	2011	F	51	No	Surgical resection	NA	No	NA
Armstrong et al. [4]	2012	F	67	Yes	Hemithyroidectomy + tracheal resection	Complete	No	7 years
	2012	M	40	Yes	Total thyroidectomy + tracheal resection	Complete	No	Lived 14 years
	2012	M	60	Yes	Total thyroidectomy	NA	NA	NA
Yu et al. [38]	2013	F	30	Yes	Hemithyroidectomy + subtotal thyroidectomy on other side	NA	No	39
	2013	M	47	Yes	Hemithyroidectomy	Complete	No	47
	2013	F	37	No	Hemithyroidectomy + isthmus + partial thyroid lobectomy on other side	Complete	No	10
Filipovic et al. [39]	2014	F	69	Yes	Extended total thyroidectomy	Complete	No	3 years
Navaratne et al. (case study)	2016	M	55	Yes	Hemithyroidectomy	Incomplete	No	4 years

bilat bilateral, *CBT* carotid body tumour, *Met* metachronous, *NA* not available, *RT* radiotherapy, *Syn* synchronous, *TT* total thyroidectomy

his presentation seemed asymptomatic, he did indeed have symptoms of an enlarged neck and some compressive type symptoms including some breathing difficulty. Previous medical and family histories were non-contributory. Ear, nose and throat examination, including direct laryngoscopy, was unremarkable. Palpation of the neck revealed a bulky left lobe of thyroid. Routine laboratory tests including thyroid function tests were all within normal limits, however he was noted by his medical officer to have persistently raised CRP (25 mg/L) and ESR (39 mm/h).

Chest radiograph was unremarkable except for right tracheal deviation. The ultrasound scan revealed a large mass replacing most of the superior aspect of the left lobe which was diffusely hypoechoic and irregular in outline. Extensive vascularity throughout the left lobe with extensive collateral vessel formation and retrosternal extension beyond the thyroid gland was also noted.

CT neck and chest confirmed the presence of a large soft tissue mass in the left side of the neck, which appeared to be growing beyond the limits of the left lobe of the thyroid. The mass measured $8.5 \times 8.0 \times 6.5$ cm and was

heterogeneously enhancing with an area of central low density suggestive of necrosis and several coarse calcifications (Figs. 1, 2). The mass extended posteriorly to contact the anterior margin of upper thoracic vertebrae and displaced the trachea to the right. There were no definite signs of invasion, enlarged local lymph nodes or metastatic disease in the chest.

No attempt at pre-operative diagnosis with fine needle aspiration (FNA) or core needle biopsy was made and the patient was booked for an elective left thyroid lobectomy. The mass was very large, extremely vascular and fibrotic. Excision of the mass was difficult because surgical planes could not easily be identified. The left recurrent laryngeal nerve was accidentally severed during the operation and there was significant blood loss (post-operative haemoglobin concentration 82 g/l).

Macroscopically, the specimen measured $11 \times 8.0 \times 5.2$ cm and weighed 122 g. On slicing, the parenchyma appeared calcified and showed a vaguely nodular cut surface. Pale fibrotic and calcified areas adjacent to the brown, fleshy homogenous thyroid parenchyma

Fig. 1 Pre-operative computed tomography scan (coronal section) with *contrast* showing abnormal vascularity of this tumour

Fig. 2 Pre-operative *CT neck* showing heterogeneously enhancing mass with area of central low density suggestive of necrosis and several coarse calcifications. The mass extends posteriorly to contact the anterior margin of upper thoracic vertebrae and displaces the trachea to the *right*. *T* trachea, *M* mass

were seen. Microscopically, the thyroid lobe showed an unencapsulated tumour with lobular architecture and intersecting bands of fibrovascular connective tissue (Fig. 3a). The tumour islands demonstrated an alveolar and organoid arrangement ('zellballen') of neoplastic cells with pink granular cytoplasm and round to ovoid nuclei (Fig. 3b). Scattered tumour cell nuclei appeared enlarged, hyperchromatic with bizarre shapes. The tumour was noted to be highly vascularised (Fig. 3c). Importantly, the tumour was seen close to blood vessels, however no tumour fragments were seen within vascular lumina. Tumour did extend to the resection margins and was seen to extend outside the thyroid. The differential diagnosis at this stage included a medullary thyroid carcinoma (MTC), a paraganglioma and a carcinoid tumour.

Immunohistochemically the tumour was positive for CD56 and synaptophysin (Fig. 4a, b). S100 highlighted scattered cells within the tumour and had a nuclear and cytoplasmic staining pattern (sustentacular cells) (Fig. 4c). The tumour was negative for cytokeratin AE1/3, CAM5.2, thyroid transcription factor 1 (TTF-1), inhibin, calcitonin, thyroglobulin and carcinoembryonic antigen (CEA). The overall morphological and immunohistochemical features were those of a paraganglioma, highlighting the essential role of immunohistochemistry in its diagnosis [2, 9, 22].

The patient was seen in clinic 11 days later. He had poor voice quality and was quite 'breathy'. Nasendoscopic examination confirmed left vocal cord palsy, with the cord in the abducted position.

Post-operative CT scans and magnetic resonance imaging (MRI) of the neck with gadolinium identified residual enhancing tissue, with ill-defined margins, anterolateral to the left side of the trachea measuring 4.5×3.2 cm in maximal axial dimensions. There was less compression on the trachea compared to pre-operative imaging and no cervical lymphadenopathy was noted. Positron emission tomography–computed tomography (PET–CT) scan showed no evidence of metastatic disease.

The patient is being followed up at the tertiary referral centre, where he has been closely monitored by 6–12 monthly MRI. 48 months after his surgery he is alive and well with no evidence of disease progression. No plans for radiotherapy have been made at this stage.

Discussion

Thyroid paragangliomas are extremely rare tumours. To date, including this case, 46 cases of PTPGs have been reported in the literature (Table 1). Forty of these cases

Fig. 3 Histology. **a** Low power ($\times 2$) of tumour with inked resection margin showing a vague lobular architecture of the tumour and intersecting bands of fibrous tissue. **b** Medium power ($\times 10$) of tumour showing alveolar and organoid cellular arrangements of

neoplastic cells embedded within hyalinized stroma. **c** High power ($\times 40$) showing vascularity of the tumour and the neoplastic cells with eosinophilic cytoplasm and round/ovoid nuclei with granular chromatin material

Fig. 4 Immunohistochemistry. **a** CD56 (neuroendocrine marker) positive ($\times 20$). **b** Synaptophysin (neuroendocrine marker) positive ($\times 20$). **c** Spindle-shaped sustentacular cells positive for S-100 protein ($\times 40$)

occurred in females, with the majority between the ages of 40–60 at diagnosis (mean 48.7 years, range 9–78 years). We report a case of PTPG in a male patient which showed local invasion into surrounding tissues. The whole tumour could not be resected which will have further implications on management of this patient. This case emphasises the need to consider PTPG in the differential diagnosis of any thyroid mass (even in those involving men or behaving in a locally aggressive fashion).

The exact cell origin of PTPG is unclear as paraganglionic tissue is not native to the thyroid gland. Displacement of the inferior laryngeal paraganglion to within the thyroid gland as a normal anatomical variant may be the cause of the rare finding of a primary intrathyroidal paraganglioma. Indeed, it has been documented that paraganglia of the inferior larynx have been found within the thyroid capsule [40]. Moreover, one of the cases included in Table 1 was originally reported as a laryngeal paraganglioma with a large portion of the tumour present within the left lobe of the thyroid [17]. This hypothesis is also supported by the matching female predominance of laryngeal paragangliomas to PTPGs [5].

The majority of cases present as a neck mass, often slowly enlarging, which can rarely be tender [14, 15, 28]. Eight cases presented as a solitary thyroid nodule [14, 15, 21–23, 26, 31, 36], of which only one was

documented as being a hot nodule detected by ^{99m}Tc pertechnetate (^{99m}Tc) scintigraphy [31]. Even though neck mass was the most common presentation, only 5 cases reported compressive symptoms, which mainly included tracheal compression [4, 5, 19, this case study]. Interestingly, 8 cases describe a history of hypertension [2, 5, 10, 18, 22, 26, 28, 29], with one reporting a normalisation of pulse and blood pressure after resection of the PTPG [26].

In terms of the natural history of PTPGs, of the 46 cases described, only sixteen distinctly describe local invasion of the tumour beyond the thyroid gland and there have been four cases reporting the presence of multicentric disease [10, 14, 16, 21]. Although there have been no reports of metastases from PTPGs [2, 4–8, 10–39], due the limited number of cases, we still recommend full staging of this tumour, including screening for other head and neck PGs. Although local extension is not regarded as a malignant feature in PTPGs [5], the frequency of this has perhaps been underestimated in the past. Eight cases report extension into the trachea or larynx [4, 5, 17–20, 39], with three invading the oesophagus [2, 5, 19] and three invading the recurrent laryngeal nerve [2, 8, 38]. Interestingly, three case reports describe vascular invasion by the tumour [4, 38]. Only two of these cases were followed up (39 months in a 30 year old female and 8 years in a

67 year old female) with no evidence of local recurrence or metastases reported. A study of the pathologic features of 120 adrenal and extra-adrenal paragangliomas identified that vascular invasion and/or extensive local invasion occurred more frequently in malignant tumours, however was not shown to be amongst the four most predictive features of malignancy [41].

Pre-operative investigation of a thyroid mass usually takes the form of radiological assessment with or without FNA. In Fig. 1, a contrast enhanced CT scan of the neck, the abnormal vasculature demonstrated should alert the clinician to consider a wide differential diagnosis. Appreciation of the prolific vascular anatomy in the pre-operative scans may have avoided or helped predict the complication of blood loss endured in this case. From the cases where FNA were performed, the outcome appears to be either non-diagnostic or yield an excessive amount of blood, atypical features suspicious for malignancy, or incorrectly diagnose MTC. Indeed, there has only been one report of diagnosing paraganglioma on FNA of a thyroid mass [6]. FNA diagnosis should be made with caution and include immunohistochemical exclusion of MTC and other thyroid tumours. FNA should not be dismissed on the basis of technical failure or misinterpretation as previously reported in PTPG. Indeed technically good FNA with sufficient material could be of help in the diagnosis of PTPG so long as the pathologist remains open to its diagnosis and performs the appropriate additional immunostains.

In keeping with many of the cases reported in the literature, histopathological features usually indicate MTC. This is because microscopically both diagnoses may show clustering of cells with granular cytoplasm and a richly vascularized stroma. In fact, these tumours may also be reported as hyalinizing trabecular adenoma, ‘atypical’ follicular adenoma and carcinoid tumours that have metastasized to the thyroid, again highlighting the essential role of immunohistochemistry in deriving the correct diagnosis [2, 9, 22]. Negative staining for cytokeratin AE1/3, calcitonin, thyroglobulin, TTF-1, inhibin and CEA but positive for chromogranin A, synaptophysin and S100 (highlighting sustentacular cells) confirms the diagnosis.

Due to the rarity of this tumour, few case reports and that the mean follow up period from the literature is only 31 months; our knowledge of the natural history of PTPGs is limited. First line management is complete resection of the tumour, however this is not always possible. There have been no reports of local recurrence following complete excision of PTPG in the literature. Besides our case, there are only two other case reports where the tumour was incompletely excised [2, 29]. Radiotherapy was planned post-operatively in a 63 year-old female, who had incomplete excision of a PTPG that had infiltrated surrounding tissues, including the recurrent laryngeal nerve and

oesophagus [2]. No mention was made of whether this actually took place or its success. There are very limited reports of the use of radiotherapy (either as primary or adjunctive therapy) in PTPG, and in fact only 3 cases are documented. In the first case, radiotherapy was the only treatment modality, with the patient being alive and well at 16 months [10]. The second case, describes a 52 year old female with extensive local invasion of PTPG [5]. The patient underwent radiotherapy treatment between two separate surgeries. As the second surgery achieved clear resection margins, it is difficult to comment on the effectiveness of the radiotherapy treatment in this case. Finally, the third case is mentioned above [2]. A recent systematic review of the efficacy of external beam radiotherapy (EBRT) in jugular and vagal PGs in 461 patients showed that long-term control of disease was achieved in nearly 90 % of cases [42]. Even though risk of radiation-induced malignancy is low, acute and late toxicities secondary to radiotherapy contribute to further morbidity [43].

In this case of incomplete resection following surgery, we propose an alternative management plan of careful long-term follow-up with imaging at 6 monthly intervals initially, increasing to yearly studies to monitor residual disease. From limited cases, it is generally accepted that there is a good prognosis following complete excision of the tumour, however it is unclear how residual tumour following debulking will behave.

Compliance with Ethical Standards

Conflict of interest None.

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