Case report

Primary paraganglioma of thyroid gland: a clinicopathologic and immunohistochemical study with review of the literature

Paraganglioma primitivo della tiroide: studio clinicopatologico e immunoistochimico con revisione della letteratura

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SUMMARY

Primary paraganglioma of the thyroid is a very rare neuroendocrine tumour. Only 24 cases have been reported in the Literature. A case of a primary paraganglioma of the thyroid is presented in order to provide a review of the Literature, an update on current knowledge and to emphasize the key diagnostic role of immunohistochemistry. A 63-year-old female presented with a 6-month history of right-sided solitary thyroid nodule. Ultrasonography and fine needle aspiration biopsy were not diagnostic. The patient underwent right hemithyroidectomy. The tumour cells showed a strongly positive staining for chromogranin A, synaptophysin and neuron specific enolase, whereas S-100 protein was positive in sustentacular cells. A diagnosis of primary paraganglioma of the thyroid was made. Radiotherapy for suspected local tumour persistence was planned. At 18-months follow-up, the patient is alive without evidence of recurrence. This case highlights the need to include primary paraganglioma of the thyroid in the differential diagnosis of neuroendocrine intra-thyroidal tumours. Immunohistochemistry is essential for diagnosis. Surgery is the treatment of choice.

KEY WORDS: Thyroid tumours • Paraganglioma • Neck mass • Differential diagnosis • Neuroendocrine tumours

RIASSUNTO

Il paraganglioma primitivo della tiroide (PTPG) è un rarissimo tumore neuroendocrino. In Letteratura ne sono stati descritti appena 24 casi. Questo caso è stato presentato al fine di evidenziare il ruolo chiave dell'immunoistochimica nella fase diagnostica ed al fine di realizzare una revisione della Letteratura e un aggiornamento sulle attuali conoscenze. La paziente è una donna di 63 anni, giunta alla nostra osservazione in seguito alla comparsa, da circa 6 mesi, di un nodulo solitario a carico dell'emitiroide destra. L'ecografia e l'ago-aspirato risultarono non dirimenti ai fini diagnostici. La paziente fu sottoposta ad un'emitiroidectomia destra. Lo studio immunoistochimico evidenziò una marcata positività delle cellule tumorali per la cromogranina A, la sinaptofisina e l'enolasi neurono-specifica, mentre le cellule di sostegno risultarono positive per la proteina S-100. Tale indagine permise di formulare la diagnosi di PTPG. La paziente fu sottoposta ad un ciclo di radioterapia post-operatoria nel sospetto di una persistenza locale di malattia. A 18 mesi dall'intervento, non sono state evidenziate recidive. In conclusione, il PTPG va incluso nella diagnosi differenziale dei tumori tiroidei. L'immunoistochimica è fondamentale ai fini diagnostici. La chirurgia rappresenta il trattamento di scelta.

PAROLE CHIAVE: *Tumori tiroidei • Paraganglioma • Tumefazioni del collo • Diagnosi differenziale • Tumori neuroendocrini*

Acta Otorhinolaryngol Ital 2009;29:97-102

Introduction

Paragangliomas (PGs) are uncommon neuroendocrine tumours, arising from the neural crest-derived paraganglia of the autonomic nervous system. Extra-adrenal paraganglia which are histochemically non-chromaffin, are related to the parasympathetic system and are located primarily in the head and neck region, the superior mediastinum and the retroperitoneum [1-3].

In the head and neck region, paraganglia are present as paired orbital, jugulo-tympanic, laryngeal, vagal and carotid bodies. PGs of the head and neck region account for 0.012% of all head and neck tumours. The carotid body and *glomus jugulare* account for more than 80% of the cases [4]. Although the thyroid gland is one of the anatomic sites in which paraganglia are not normally located, a few cases of primary thyroid PGs (PTPGs) have been reported in the literature. Due to their rarity and potentially malignant behaviour, PTPGs often present a difficult diagnostic problem, both for the otolaryngologist and the pathologist. With rare exceptions, they are endocrinologically silent [3].

In the present report, an unusual case of an intra-thyroidal PG presenting as a solitary thyroid nodule is described. The clinical and histological findings, as well as the problems related to the differential diagnosis and treatment are discussed.

Case report

A 63-year-old female was admitted to our Otorhinolaryngology Unit for a non-tender right-sided solitary thyroid nodule, of unknown duration, which was incidentally discovered during an ultrasound (US) examination of the neck. There was no past history of thyroid disorders or neck irradiation. Family history was unremarkable, particularly regarding thyroid diseases. The medical history of the patient was negative except for light hypertension and cholelithiasis. Physical examination revealed a painless, well-circumscribed, solid mass in the right lobe of the thyroid, without palpable cervical adenopathy and with normal laryngeal motility.

Ultrasonography (US) showed a 4 cm, hyperechoic, non-homogeneous nodule in the right thyroid lobe with remarkable peri- and intra-nodular vascular flow; no nodules in left lobe, nor cervical lymph node enlargement were evident. Serum, Thyroid Stimulating Hormone (TSH), T3, T4, calcitonin, and thyroglobulin were within normal limits.

US-guided fine needle aspiration biopsy (FNAB) of the nodule was performed. Although the presence of atypical cells was demonstrated, cell morphology was not helpful for diagnosis. The patient underwent surgical resection of the right thyroid lobe; debulking was very difficult, due to the presence of a firm neoplasm that spread beyond the gland capsule with infiltration of the surrounding tissues, in particular the laryngeal recurrent nerve, the muscles and the oesophagus. A transitory right vocal cord palsy occurred, without need of tracheotomy as it regressed after 10 days with steroid treatment. Neither lymph node enlargement, nor multi-centric disease were observed.

Conventional histology and immunohistochemistry studies were performed.

Conventional histology was performed on formalin-fixed and paraffin-embedded tissue blocks; 4 µm sections were cut, deparaffinized in xylene and stained with haematoxylin and eosin (H&E).

Histologic examination revealed a poorly circumscribed neoplasm with a nesting pattern ("Zellballen"), composed of large cells, with moderately pleomorphic nuclei containing variably sized nucleoli and eosinophilic granular cytoplasm (Figs. 1, 2). The stroma was scanty, with numerous blood vessels. The tumour was not encapsulated and infiltrated the surrounding thyroid tissue.

The immuno-staining procedure was performed on xylene-deparaffinized slides employing an automated stainer (DAKO Cytomation Autostainer, DAKO-Italia, Milan, Italy), at room temperature, using the peroxidase anti-peroxidase method according to the manufacturer's instructions. The following antibodies to various antigens were tested at the proper dilution as shown in Table I. Her-2/neu oncoprotein study was immunohistochemically performed using the standardized HERCEP Test Kit (DAKO-Italia, Milan, Italy).

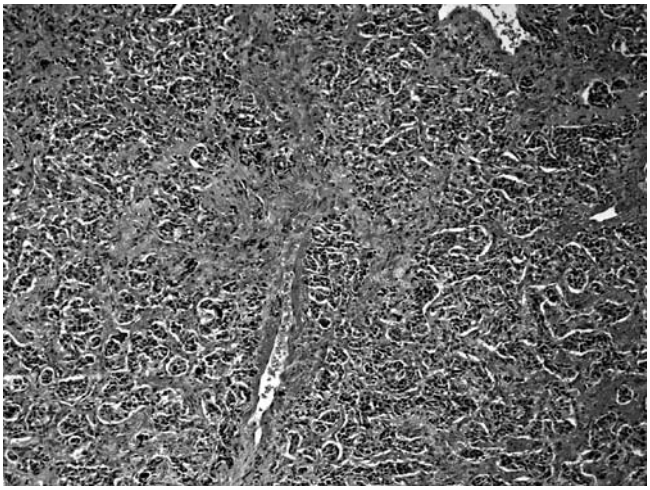

Fig. 1. Tumour exhibits variably sized nests in a vascularized stroma (Haematoxylin and Eosin, [H&E], X10, orig. magn.).

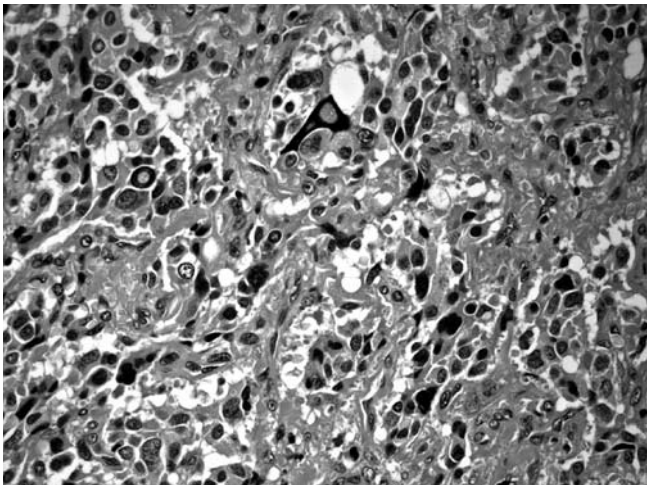

Fig. 2. Cellular detail showing moderately pleomorphic tumour cells embraced by sustentacular cells (H&E, X40, orig. magn.).

The tumour cells showed a strongly positive staining for chromogranin A, synaptophysin, and neuron specific enolase. S-100 protein reactivity was detected in sustentacular cells located at the periphery of the tumour cell nests (Fig. 3) whereas no immunoreactivity was detected for calcitonin, carcinoembryonic antigen (CEA), cytokeratin 19, thyroglobulin, TTF-1 (Thyroid Transcription Factor-1) and Her-2/neu oncoprotein. Proliferative activity of the neoplasm, studied by immunohistochemical staining with the cell proliferation marker Ki-67 was low. In fact, less than 5% of the neoplastic cells showed nuclear staining indicating proliferative activity. The diagnosis of thyroid

Table I. Antigen retrieval method.

Antigen	Clone	Manufacturer	Dilution	Type of antigen retrieval method
Calcitonin	CAL-3_F5	DakoCytomation*	1:50	None
CEA (Carcinoembryonic Antigen)	II-7	DakoCytomation	1:50	Heat-induced epitope retrieval with citrate buffer, pH 6.0
Chromogranin A	DAK-A3	DakoCytomation	1:200	Heat-induced epitope retrieval with target solution, high pH
Cytokeratin 19	–	Neomarker**	1:50	Pre-treatment with proteolytic enzymes
Ki67	MIB-1	DakoCytomation	1:100	Heat-induced epitope retrieval with target solution, high pH
NSE (Neuron-Specific Enolase)	BBS/NC/VI-H14	DakoCytomation	1:50	Heat-induced epitope retrieval with citrate buffer, pH 6.0
S-100	–	DakoCytomation	1:400	Pre-treatment with proteolytic enzymes
Synaptophysin	–	DakoCytomation	1:100	Heat-induced epitope retrieval with citrate buffer, pH 6.0
Thyroglobulin	–	DakoCytomation	1:2000	None
TTF-1 (Thyroid Transcription Factor-1)	8G7G3/1	Neomarker	1:50	Heat-induced epitope retrieval with citrate buffer, pH 6.0

*Immunohistochemical study and antigens tested (*DakoCytomation, DAKO-Italia, Milan, Italy; **Neomarker, Fremont, CA, USA).*

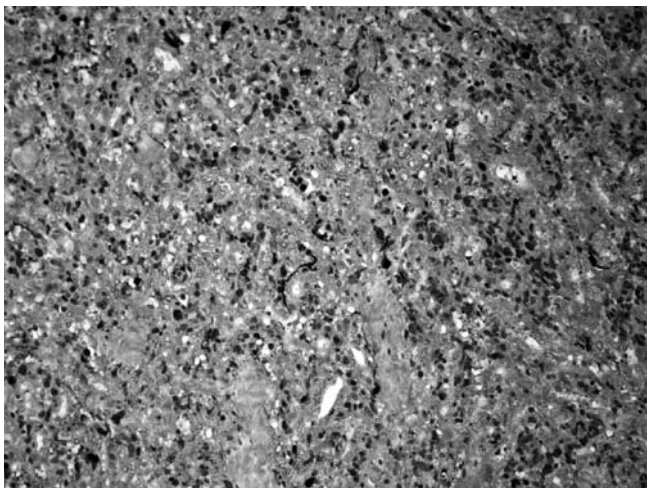

Fig. 3. A dendritic pattern is focally evident with S-100 protein immunostaining due to presence of sustentacular cells (X20, orig. magn.).

paraganglioma was made on the basis of the overall histological and immunohistochemical features.

Following the pathology report, a total-body computed tomography (CT) was performed which did not demonstrate any evidence of multicentric tumour or distant metastases. Magnetic resonance imaging (MRI) of the neck showed the presence of enhancing, hypervascular tissue in front of the oesophagus. The patient was discharged 8 days after surgery. Radiotherapy was planned due to suspicion of local residual tumour. At 18 months' follow-up, the patient is alive without evidence of recurrence.

Discussion

The first reported PTPG was described by Van Miert in 1964 [5]. Since then, to our knowledge, only 24 cases have been reported in the Literature (Tab. II) [5-24]. All the cases reported, except two, occurred in females aged between 9 and 73 years. PTPG occurred only in 4 cases in association with a synchronous carotid body tumour [5 6 9 14] and in one case with a parathyroid adenoma and a papillary carcinoma [7]. Most PGs are confined within the thyroid capsule but in 3 cases the neoplasm was locally invasive and infiltrated through the tracheal wall [10 11 13]. Also in our case, the tumour spread beyond the thyroid capsule with infiltration of the laryngeal recurrent nerve. Debulking was very difficult and a transitory laryngeal paralysis occurred.

The clinical and morphologic features of PTPG closely mimic those of more common thyroid lesions. Clinically, most affected patients have an asymptomatic and non-functional intra-thyroidal nodule of several years' duration. As in our case, these long-standing thyroid nodules are dismissed as nodular goitre, thyroglossal duct cyst or follicular adenoma [9 12].

The histological diagnosis of PTPG may be very difficult.

Differential diagnosis includes two main entities, namely hyalinizing trabecular adenoma of the thyroid (HTAT) (also called paraganglioma-like adenoma) and medullary carcinoma of the thyroid (MCT), especially when it exhibits a nesting (paraganglioma-like) pattern of growth. Furthermore, before accepting a diagnosis of PTPG, the third alternative must be considered concerning a PG of the carotid body or other cervical PG that has grown in close proximity to the thyroid or even extended into the thyroid. This latter distinction is entirely dependent upon the surgical and gross findings [25]. The criteria of malignancy in PTPGs are a controversial subject and include metastasis, necrosis, uniform cytological atypia and vascular invasion. Unlike malignant neoplasms elsewhere, local infiltration, as in our case, is not indicative of malignancy in PTPGs. In all reported cases, including ours,

Table II. Primary paraganglioma of thyroid. Review of 24 cases reported in Literature.

Author (ref.)	Cases	Sex	Age (yrs)	Surgery and/or other treatment	Follow-up	Multicentric disease
Van Miert [5]	1	F	63	Radiotherapy	?	Synchronous carotid body tumour
Haegert [6]	1	F	36	Left hemithyroidectomy	Alive and well 5 years	Bilateral carotid body tumour
Massaioli [7]	1	F	9	Subtotal thyroidectomy	Alive and well 5 months	–
Banner [8]	1	F	36	Left lobectomy	?	–
Buss [1]	1	F	50	Left hemithyroidectomy	Alive and well 30 months	
Cayot [9]	1	F	58	Total thyroidectomy	?	Bilateral carotid body tumour Parathyroid adenoma Papillary carcinoma
Olofsson [10]	1	F	44	Left lobectomy + partial pharyngectomy + total laryngectomy + partial tracheal resection	Alive and well 7 years	–
Mitsudo [11]	1	F	50	Total thyroidectomy + segmental anterior resection of trachea	Alive and well 2 years	–
de Vries [12]	1	F	73	Left hemithyroidectomy	Alive and well 2 years	–
Brownlee [13]	1	F	27	Right lobectomy + right subglottic laryngectomy	Alive and well 18 months	–
Hughes [14]	1	F	50	Total thyroidectomy	Alive and well 2 years	Synchronous carotid body tumour
LaGuette [15]	3	F F F	55 64 56	Total thyroidectomy; Left hemithyroidectomy; Right hemithyroidectomy	Alive and well at 4, 7 and 8 years, respectively	– – –
Tiong [16]	1	F	52	Left lobectomy	Alive and well 2 years	–
Kronz [17]	2	M F	55 52	Left lobectomy + isthmusectomy; Total thyroidectomy + radiotherapy	Alive and well at 9 months and 6 years, respectively	–
Napolitano [18]	1	F	47	Total thyroidectomy	Alive and well 6 months	–
Skiadas [19]	1	F	54	Total thyroidectomy	Alive and well 22 months	–
Vera–Cruz [20]	1	F	32	Right hemithyroidectomy	Alive and well 4 years	–
Vodovnik [21]	1	F	46	Right lobectomy	–	
Corrado [22]	1	F	46	Right lobectomy + isthmusectomy	–	
Zantour [23]	1	F	32	Total thyroidectomy + resection of cricoid cartilage	Alive and well 6 years	–
Yano [24]	1	M	24	Right lobectomy	Alive and well 6 months	–

there was no evidence of recurrence or metastatic disease following total surgical excision [17 26].

Not surprisingly, the diagnosis of PTPG is rarely established pre-operatively by FNAB or intra-operatively by frozen section. Because the tumours included in the differential diagnosis are morphologically similar, immunohistochemistry is essential in distinguishing PTPG from MCT and HTAT. The histopathological features of PTPG usually suggest MCT. This is due to the clustering of cells with granular cytoplasm (positive for chromogranin A, synaptophysin and neuron specific enolase) and a richly vascularized stroma, features which are indicative of either MCT or PTPG. In contrast with most MCT, however, PTPGs tend to exhibit S-100 protein staining in sustentacular cells compressed at the periphery of the cell nests and they lack staining for cytokeratin, CEA and calcitonin. Unfortunately, some laryngeal PGs are calcitonin positive and, conversely, some

MCT contain S-100 positive sustentacular cells [15 22 27]. Furthermore, an unusual variant of MCT, such as that showing clusters of tumour cells aggregated as "Zellballen" (paraganglioma-like variant), may be distinguished from PG just by positive immunostaining for calcitonin and CEA and by histochemical detection of amyloid deposits with Congo Red stain [28]. Other markers reported in MCT, in the literature, include TTF-1 [29] and Her-2/neu expression [30]. Remarkably, our PG case was negative for the above markers. Other cases of PTPG need to be tested in order to confirm our results, possibly useful in distinguishing between MCT and PTPG.

Concerning the differential diagnosis of PTPG from HTAT, the latter exhibits a characteristic trabecular pattern, with occasional follicles and with prominent hyaline extra- and intra-cellular deposits and shows positivity for thyroglobulin immunostaining, although – like PTPG – is negative for calcitonin and may express neuroendocrine markers such as chromogranin A and neuron specific enolase [25].

Although very rare cases with metastasis have been reported, the clinical course of PGs, in other sites of the head and neck, is also known to be generally benign. Total thyroidectomy or even thyroid lobectomy with long-term follow-up are the preferred treatment options in PTPGs. Elective neck dissection is not indicated. None of the previously reported cases of thyroid PG was associated with metastasis, but, in some cases, this neoplasm was associated with bilateral or mono-lateral carotid body tumours [12 14 15]. The prognosis of PTPG appears to be favourable, provided that surgical excision is complete. The use of serum calcitonin and CEA levels to monitor residual or recurrent disease is unwarranted. Radiation therapy is used only when surgery is not feasible or when local persistence of the tumour is suspected after surgery.

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Received: February 27, 2008 - Accepted: June 08, 2008

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