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

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. In the head and neck region, paraganglia are present as paired orbital, jugulo-tymppanic, 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. 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 otorhinolaryngologist and the pathologist. With rare exceptions, they are endocrinologically silent.
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).

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
Primary paranglioma of thyroid

paranglioma was made on the basis of the overall histo-
logical and immunohistochemical features.
Following the pathology report, a total-body computed to-
mography (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 lo-
cal 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 associa-
tion 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 cap-
sule 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 infiltra-
tion 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’ dura-
tion. 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 diffi-
cult. Differential diagnosis includes two main entities, namely
hyalinizing trabecular adenoma of the thyroid (HTAT)
(also called paranglioma-like adenoma) and medullary
carcinoma of the thyroid (mCT), especially when it ex-
hibits a nesting (paranglioma-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 malig-
nancy in PTPGs are a controversial subject and include
metastasis, necrosis, uniform cytological atypia and vas-
cular invasion. Unlike malignant neoplasms elsewhere,
local infiltration, as in our case, is not indicative of mal-
ignancy in PTPGs. In all reported cases, including ours,
there was no evidence of recurrence or metastatic disease following total surgical excision.

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

<table>
<thead>
<tr>
<th>Author (ref.)</th>
<th>Cases</th>
<th>Sex</th>
<th>Age (yrs)</th>
<th>Surgery and/or other treatment</th>
<th>Follow-up</th>
<th>Multicentric disease</th>
</tr>
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<tbody>
<tr>
<td>Van Miert</td>
<td>5</td>
<td>F</td>
<td>63</td>
<td>Radiotherapy</td>
<td>?</td>
<td>Synchronous carotid body tumour</td>
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<tr>
<td>Haegert</td>
<td>6</td>
<td>F</td>
<td>36</td>
<td>Left hemithyroidectomy</td>
<td>Alive and well 5 years</td>
<td>Bilateral carotid body tumour</td>
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<td>Massaoli</td>
<td>7</td>
<td>F</td>
<td>9</td>
<td>Subtotal thyroidectomy</td>
<td>Alive and well 5 months</td>
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<tr>
<td>Banner</td>
<td>8</td>
<td>F</td>
<td>36</td>
<td>Left lobectomy</td>
<td>?</td>
<td>–</td>
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<td>Buss</td>
<td>1</td>
<td>F</td>
<td>50</td>
<td>Left hemithyroidectomy</td>
<td>Alive and well 30 months</td>
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<td>Cayot</td>
<td>8</td>
<td>F</td>
<td>58</td>
<td>Total thyroidectomy</td>
<td>?</td>
<td>Bilateral carotid body tumour Parathyroid adenoma Papillary carcinoma</td>
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<td>Olofsson</td>
<td>10</td>
<td>F</td>
<td>44</td>
<td>Left lobectomy + partial pharyngectomy + total laryngectomy + partial tracheal resection</td>
<td>Alive and well 7 years</td>
<td>–</td>
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<tr>
<td>Mitsudo</td>
<td>11</td>
<td>F</td>
<td>50</td>
<td>Total thyroidectomy + segmental anterior resection of trachea</td>
<td>Alive and well 2 years</td>
<td>–</td>
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<tr>
<td>de Vries</td>
<td>12</td>
<td>F</td>
<td>73</td>
<td>Left hemithyroidectomy</td>
<td>Alive and well 2 years</td>
<td>–</td>
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<tr>
<td>Brownlie</td>
<td>13</td>
<td>F</td>
<td>27</td>
<td>Right lobectomy + right subglottic laryngectomy</td>
<td>Alive and well 18 months</td>
<td>–</td>
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<td>Hughes</td>
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<td>F</td>
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<td>Alive and well 2 years</td>
<td>Synchronous carotid body tumour</td>
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<td>LaGuetta</td>
<td>15</td>
<td>F</td>
<td>55</td>
<td>Total thyroidectomy; F 64, F 56</td>
<td>Alive and well at 4, 7 and 8 years, respectively</td>
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<tr>
<td>Tiong</td>
<td>16</td>
<td>F</td>
<td>52</td>
<td>Left lobectomy</td>
<td>Alive and well 2 years</td>
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<td>Kronz</td>
<td>17</td>
<td>M</td>
<td>55</td>
<td>Left lobectomy + isthmusectomy; Total thyroidectomy + radiotherapy</td>
<td>Alive and well at 9 months and 6 years, respectively</td>
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<td>Napolitano</td>
<td>18</td>
<td>F</td>
<td>47</td>
<td>Total thyroidectomy</td>
<td>Alive and well 6 months</td>
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<tr>
<td>Skiadas</td>
<td>19</td>
<td>F</td>
<td>54</td>
<td>Total thyroidectomy</td>
<td>Alive and well 22 months</td>
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<td>Vera–Cruz</td>
<td>20</td>
<td>F</td>
<td>32</td>
<td>Right hemithyroidectomy</td>
<td>Alive and well 4 years</td>
<td>–</td>
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<tr>
<td>Vodovnik</td>
<td>21</td>
<td>F</td>
<td>46</td>
<td>Right lobectomy</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Corrado</td>
<td>22</td>
<td>F</td>
<td>46</td>
<td>Right lobectomy + isthmusectomy</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Zantour</td>
<td>23</td>
<td>F</td>
<td>32</td>
<td>Total thyroidectomy + resection of cricoid cartilage</td>
<td>Alive and well 6 years</td>
<td>–</td>
</tr>
<tr>
<td>Yano</td>
<td>24</td>
<td>M</td>
<td>24</td>
<td>Right lobectomy</td>
<td>Alive and well 6 months</td>
<td>–</td>
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MCT contain S-100 positive sustentacular cells. 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 amylod deposits with Congo Red stain. Other markers reported in MCT, in the literature, include TTF-1 and Her-2/neu expression. 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.

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. 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.

References


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