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Case Report

Thyroid gland paraganglioma: report of a case and review of the literature

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Abstract: Background: The uncommon thyroid associated paraganglioma is supposed to be originating from the inferior laryngeal paraganglia. Differential diagnosis is most problematic, chromogranin A, synaptophysin and S100 protein are immunohistochemical markers of this tumor. Patient and method: A 66-year old woman presented with an asymptomatic left side anterior neck mass. Ultrasound-guided fine needle aspiration cytology, scintigraphy and computed tomography, magnetic resonance imaging scans showed the presence of a benign thyroid nodule. Half year later it began to grow and caused soreness. Left thyroid lobectomy was carried out and a non-Hürthle cell follicular carcinoma with positive resection margin was found. To complete total thyroidectomy, right side lobectomy and isthmus resection were done without finding any further malignancy. Pathological revision of the left lobe specimen with additional immunohistochemical examination (positive staining for chromogranin A and synaptophysin, negative staining for thyreoglobulin and calcitonin, while some of the tumor cells were S100 positive) proved the tumor to be a malignant thyroid paraganglioma. As the resection margin of the left lobectomy was positive, the patient received adjuvant radiotherapy (60 Gy/2 Gy/day to the thyroid bed). During the follow-up time (18 months) the patient is alive, with no evidence of disease. Conclusion: Since the diagnosis of paraganglioma is usually problematic, recognition of this rare entity is very important. Adjunctive immunohistochemical methods play essential role in distinguishing it from other thyroid diseases. Radiotherapy can be considered as alternative primary treatment, but it is necessary, especially for treating residual tumor.

Keywords: Thyroid gland, malignant, paraganglioma, immunohistochemistry, radiotherapy

Introduction

Paraganglioma (PGL) is a rare neuroendocrine tumor arising from extra-adrenal paraganglia along the sympathetic and parasympathetic chain. Its location can extend from the skull base to the pelvic floor, the majority arising in the abdomen (85%), superior mediastinum (12%) and head and neck (H&N) (3%) [1]. In the H&N region PGLs are named after the ganglion of origin and are frequently found next to vascular structures. Carotid body tumors are by far the most common in the H&N region, followed by glomus jugulare and vagal cases. Other rare sites where this tumor may arise from paraganglia are the nasopharynx, nasal cavity, orbit, larynx, aortic arch and thyroid gland [1-3]. The thyroid associated entity represents a subset of inferior laryngeal PGL and it can be located adjacent to or inside the gland [4]. This tumor accounts for less than 0.1% of all thyroid neoplasms and 0.012% of all H&N tumors [5]. Owing to its benign behavior, it is generally characterized by slow growth, so most patients present with an asympthomatic neck mass. Because of its rarity and non-specific clinical and histological features, thyroid PGL is easily misdiagnosed as some other common thyroid neoplasm with a different prognosis and required treatment. In the present report we wish to discuss differential diagnosis and treatment possibilities of PGL based on the literature, calling attention to its potential occurrence in the thyroid gland.

Case report

A 66-year old woman presented with an asymptomatic left side anterior neck mass. Ultrasonography revealed a solid nodule of low echogenecity located in the lower left lobe, measuring

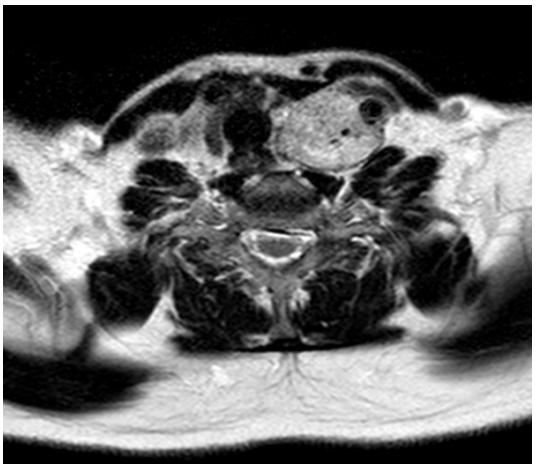

Figure 1. Axial T2 weighted magnetic resonance imaging (MRI) scan shows a 30×30 mm, highly enhanced lesion, next to the left thyroid lobe, seperated by an indistinct border.

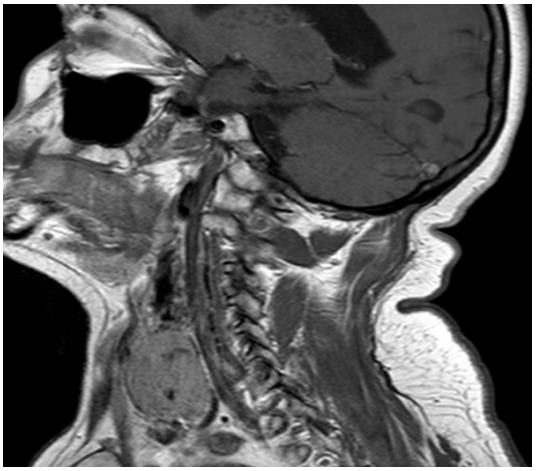

Figure 2. Sagittal T1 weighted MRI scan shows moderately high enhanced nodule, which appears to be separated from the surrounding fat tissue.

3.8×2.1 cm in size. Fine needle aspiration (FNA) showed the presence of follicular cells. Computed tomography (CT) scan demonstrated a contrast enhanced, inhomogeneous mass with low density. Magnetic resonance imaging (MRI) showed a contrast enhanced structure with an indistinct border next to the left lobe (**Figures 1**, **2**). Serum thyroid stimulating hormone (TSH) level was slightly elevated: 4.93 mIU/l. Because of the benign behavior, observation was recommended. Half year later the nodule began to grow and caused soreness. Beside general fatigue, change of appetite, casual shivering, sweat and hypotension were

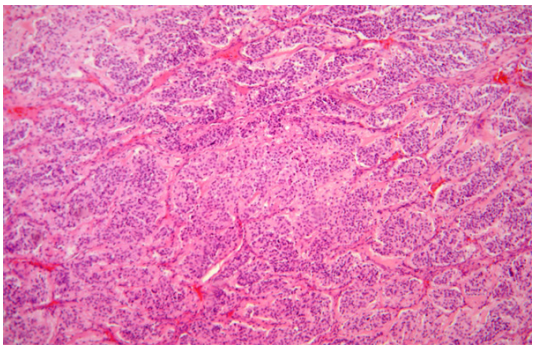

Figure 3. Paraganglioma showing the characteristic nesting pattern (Zellballen) in vascularized stroma, separated by fibrovascular septa. (Hematoxylin and eosin stain, ×100).

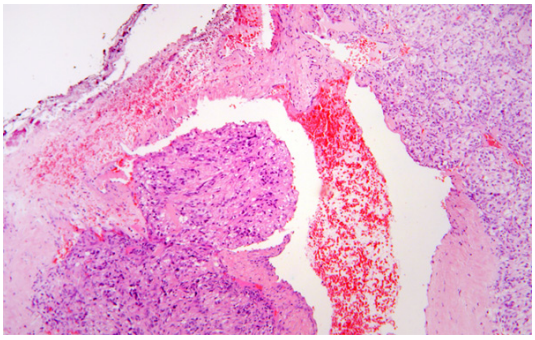

Figure 4. Paraganglioma with vascular invasion and some necrotic areas. (Hematoxylin and eosin stain, ×100).

reported by the patient. She underwent left thyroid lobectomy, and the presence of a non-Hürthle cell follicular thyroid cancer was verified. The resection margin being positive, right side lobectomy and resection of isthmus were also performed, which did not reveal further malignancy. Pathological revision of the left lobe specimen with additional immunhistochemical analysis suggested the final diagnosis: malignant paraganglioma involving the thyroid gland. Histologically, the partially encapsulated mass exhibited variably sized nests in a vascularized stroma. The nesting pattern composed of polygonal chief cells was surrounded by a trabecular architecture built up of spindle shaped sustentacular cells (**Figure 3**). Nuclei of different sizes and shapes were seen in these cells. The tumor showed invasion into the vessels, and infiltrated the capsule. Necrosis was identified in some areas (**Figure 4**). Immunohistochemical analysis helped to define the origin of the tumor. The sustentacular cells were high-

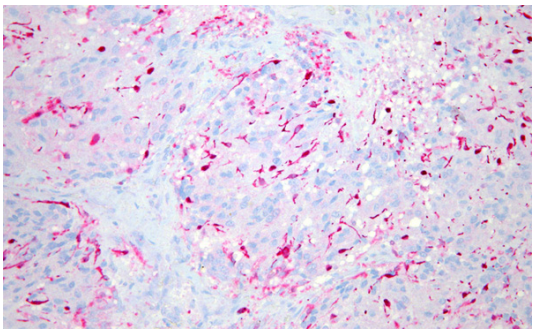

Figure 5. Paraganglioma with sustentacular cells highlighted by S-100 protein. (Immunohistochemical stain, Hematoxylin nuclear stain, ×200).

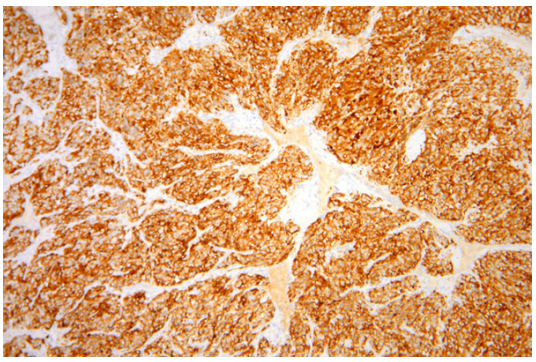

Figure 6. Paraganglioma showing diffuse positivity for chromogranin A. (Immunohistochemical stain, Hematoxylin nuclear stain, ×200).

lighted by S-100 protein (**Figure 5**). The neoplasm was positive for synaptophysin, chromogranin A, while negative for thyreoglobulin, thyroid peroxidase, calcitonin and pan cytokeratin (**Figure 6**). Postoperative CT scan of the operated region as well as of the chest, abdomen, and pelvic region did not show any residue or dissemination of the tumor. The 24 h urine vanillyl-mandelic acid (VMA) level was normal. As the resection margin of the left lobectomy was positive, the patient received adjuvant conformal radiotherapy to the operated region, up to a total dose of 60 Gy, with conventional (2 Gy/day) fractionation, during 6 weeks, from Monday to Friday. The Tumor Board did not indicate any other treatment. During the follow-up time (18 months) the patient is alive, with no evidence of disease.

Discussion

Thyroid associated PGL is an extremely rare tumor. The first case was described by Van Miert [6] in 1964. This neoplasm is supposed to be originating from the inferior laryngeal paraganglia and can be located lateral to the thyroid gland or inside it. This may be attributed to the embryonic migration pathway of neural crest cells within the thyroid capsule itself [3, 4].

Since the latest review of Bao-Hua [5] with 35 patients published in 2013, we have found 6 other cases reported in the English-language literature [7-12]. With a female predominance the mean age of the patients in these presentations was 47 years (range, 19-78 years). Most patients with thyroid PGL are asymptomatic but as the tumor grows it may become visible as an anterior neck mass, and cause dysphagia, dyspnea or hemoptysis [1]. Thyroid PGL is typically non-functional without secretion of catecholamines, thus it is believed to be associated with the parasympathetic system [2, 3]. The incidence of functional PGL in this area is only 1 to 3%, and only a single case was reported with functional thyroid associated PGL [13]. In our case, the symptoms present before the operation might point towards an origin from the sympathetic nervous system, however the hypotension may contradict this.

PGL often causes a diagnostic problem, because the disease shows no specific features either clinical or morphologic. Thyroid PGL is euthyroid with normal levels of thyroid hormones, calcitonin and carcinoembryonic antigen (CEA). Pre-operative FNA cytology and radiological examinations have been reported to have limited a value in the distinction between malignant or benign behavior of the disease [4, 5, 10, 12]. By ultrasonographic imaging the tumor is typically seen as a solid hypoechoic nodule with increased intranodular and perinodular vascular flow on color Doppler [4]. By scintigraphy the tumor usually appears as a cold nodule, only one hot nodule was reported in the literature [14]. Low density seen on CT usually refers to benign entities. MRI plays important role in the differential diagnosis, because it demonstrates hypervascularization and the border between soft tissues and vessels. Positron emission tomography (PET) is not routinely used, however 18F-6-fluorodihydroxyphenylalanine PET has been reported as a valuable functional imaging modality of succinate dehydrogenase related to the H&N PGLs [3].

Direct angiography has been reported to be used for only embolization-in order to reduce the vascularity-before surgery or palliative RT [1, 2].

Histologically, PGL typically shows a nesting "Zellballen" pattern composed by polygonal chief cells and surrounding sustentacular cells [5]. A thin, fibrous capsule is usually present. This cellular structure may be misdiagnosed as other types of thyroid neoplasms, but in combination with immunohistochemical examination, differentiation is possible in most cases. Medullary thyroid carcinoma (MTC) and hyalinizing trabecular adenoma of the thyroid (HTT) are the pitfalls of the differential diagnosis [14]. In MTC, tumor cells are usually immunoreactive for cytokeratin, thyroid transcription factor-1, neuroendocrine markers, calcitonin and carcinoembryonal antigen (CEA). Positivity of epithelial markers and the lack of S100 positive sustentacular cells also facilitate the differentiation. Unfortunately, rare cases of MTC may contain S100 positive sustentacular cells or may be negative for CEA and calcitonin, and conversely PGL may be calcitonin or cytokeratin positive, causing difficulty in making a correct diagnosis [5, 15, 16]. HTT is also called paraganglioma-like adenoma, exhibiting trabecular pattern with both prominent intratrabecular and interstitial hyaline material. It is positive for thyreoglobulin and cytokeratin, although-like PGL-is negative for calcitonin and both tumors may express chromogranin A and neuron specific enolase, making differential diagnosis problematic [3]. Other entities, like follicular neoplasm, Hürthle cell neoplasm, metastatic carcinoid tumor, secondary neuroendocrine tumor might also need attention in differentiation [3, 5, 10].

There has been no agreement yet regarding the criteria of malignancy of PGL. Histological or immunohistochemical markers are not known to differentiate benign PGL from the malignant one. It is generally accepted that the presence of metastasis to the regional lymph nodes or distant sites is the sign of the malignant nature, although in some articles necrosis, uniform cytological atypia and vascular invasion are also mentioned among the malignant features [15]. Based on data of the literature capsule invasion or local infiltration do not unambiguously indicate malignant potential [1, 8, 9].

Most of PGLs are sporadic and only 10% of them are familiar. The latter are usually multiple and show germline mutations in succinate dehydrogenase B (SDHB), C (SDHC), D (SDHD) or SDH assembly factor 2 (SDHAF2) [16]. More than half of the patients with H&N PGL have germline mutations in these genes [17]. It has also been suggested that patients with SDHB mutation have a significantly higher risk for malignancy compared to patients with SDHC and SDHD mutations or those with sporadic tumors [3, 18]. Therefore, genetic testing is highly important in PGL and for patients with SDHB mutation distant metastasis screening is recommended [13].

Synchronous and metachronous multicentric occurrence is not uncommon in PGL [15]. To date, 4 cases of thyroid PGLs were accompanied by synchronous PGLs (carotid body tumor /n=2/, bilateral carotid body tumor and glomus vagal tumor) [4]. Hence long-term follow-up by cervical ultrasonography, whole-body CT and 24 h urine hormone excess (catecholamines, metanephrines, normetanephrines) are recommended [19].

Surgery is currently considered the standard of care for primary treatment of PGL. For the thyroid associated PGL, depending on the size, multifocality and extent of involvement, subtotal or total thyroidectomy is the suggested treatment option. Elective radical neck dissection is not indicated, because until now only one case of paratracheal lymph node metastasis has been reported [20]. However, due to intraoperative atypical cytology or high risk of malignancy, the pretracheal (level VI) lymph node region of the neck has been dissected in some cases [9].

RT is commonly used as single modality treatment for nonresectable PGL or as adjuvant treatment after incomplete resection [15, 21-26]. According to the literature, RT for H&N PGL results in high tumor control and overall survival equal to surgery, with less morbidity [21, 23, 27, 28]. In the study of Dupin [26], a total of 66 patients with 81 PGLs were treated with definitive and salvage irradiation resulting in local control rates of 100% and 98.7% at 5 and 10 years, respectively. Hinerman [21] describing 121 PGLs reported a 95% cause-specific survival and local control rates at 10 years. There were less side effects and better quality of life

was achieved when the patients were treated with RT alone versus combined surgery and RT [25]. These results show that RT is an effective and well tolerated method, so it can be considered as a first-line choice for H&N PGL.

There are few data available about optimal dose and treatment technique of RT. Pecak [22] evaluated the correlation between total dose and overall survival. Significantly higher 5-year overall survival was found in the group of patients who received 60 Gy or higher doses compared with those receiving less than 60 Gy (92% vs. 70%). In addition to 3D conformal and intensity modulated RT (IMRT) technique recent studies have advocated for stereotactic radiosurgery in cases of small or unresectable tumor, where conventional fractionated RT is not recommended. However, more studies and longer follow up duration are needed to make any substantive conclusion [21].

To date only a single case of PGL treated with chemotherapy, peptide receptor radionuclide therapy and permanent TSH suppressive therapy after total thyroidectomy has been reported in the literature [11].

As PGL is a slow growing benign tumor, small, asymptomatic PGL should be rather observed, and the benefits of treatment have to be weighed against life expectancy. Hence the optimal treatment strongly depends on tumor size, localization and side effects [2, 29]. To our knowledge, evidence of recurrence, metastasis or deaths have not been reported in association with thyroid PGL.

In conclusion, our case report confirms that diagnosis of this rare entity is usually problematic, although immunohistochemical methods play a significant role in distinguishing thyroid PGL from other thyroid gland diseases. RT can be considered as alternative primary treatment, and especially for treating residual tumor. Because of its multicentric nature and uncertain malignant potential, long-term follow up is recommended. Genetic testing is also advisable to be performed.

Disclosure of conflict of interest

None.

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