Head and Neck Pathol
DOI 10.1007/s12105-009-0157-7

CASE REPORT

Primary Paraganglioma of the Parathyroid: A Case Report and Clinicopathologic Review

Michael T. Levy · John T. Braun · Marjorie Pennant · Lester D. R. Thompson

Received: 26 October 2009 / Accepted: 3 December 2009

Abstract Paragangliomas are relatively uncommon neoplasms that arise in adrenal and extra-adrenal paraganglia of the autonomic nervous system. Parasympathetic paraganglioma develop predominantly in the head and neck. It is exceedingly uncommon to develop a primary intraparathyroid paraganglioma. There is only a single case report in the English literature. The information from the single previous case report (Medline 1960–2009) was combined with this case report. Our patient was a 69 year old woman who presented with a thyroid gland mass, with extension into the substernal space. The patient had a history of renal cell carcinoma removed 18 months before. At surgery, a thyroid lobectomy and a parathyroidectomy were performed. The parathyroid tissue showed a very well defined zellballen arrangement of paraganglion cells within the parenchyma of the parathyroid gland. The cells had ample basophilic, granular cytoplasm. The nuclei were generally round to oval with 'salt-and-pepper' nuclear chromatin distribution. There was a richly vascularized stroma. Mitotic figures, necrosis, invasive growth, and profound nuclear pleomorphism were absent. The neoplastic cells were strongly and diffusely immunoreactive with chromogranin, synaptophysin, CD56, and focally with cyclin-D1. The paraganglioma showed a delicate S-100 protein positive supporting sustentacular framework. Keratin, CD10, PTH, calcitonin and RCC markers were negative. The patient showed no stigmata of Multiple Endocrine Neoplasia (MEN) and has no paraganglioma in any other anatomic site. She is alive without any additional findings 12 months after surgery. Isolated paraganglioma within the parathyroid is rare, and should be separated from parathyroid adenoma, hyperplasia or metastatic disease to assure appropriate management.

Keywords Parathyroid · Paraganglioma · Immunohistochemistry · Management · Review · Metastatic disease · Parathyroid adenoma · Parathyroid hyperplasia · Chromogranin

Introduction

Paraganglioma is a tumor that develops from the paraganglionic system. While the preponderance of paraganglionic tissue is identified within the adrenal gland medulla, the extra-adrenal paraganglia are distributed throughout the body. Extra-adrenal paraganglia can be divided into sympathetic and parasympathetic types depending upon their usual site of development. While indistinguishable histologically, they differ in their secretory products. The sympathetic paraganglia are found primarily along the axial trunk in the prevertebral and paravertebral sympathetic chains, as well as in and around pelvic organs. Parasympathetic paraganglia differ by being identified almost exclusively in the head and neck region [1]. Parasympathetic tumors tend not to produce catecholamines as part of their clinical manifestations, and seem to be more frequently associated with hypoxemia. Parasympathetic tumors also

M. T. Levy · L. D. R. Thompson (✉)
Department of Pathology, Southern California Permanente Medical Group, Woodland Hills Medical Center, 5601 De Soto Avenue, Woodland Hills, CA 91365, USA
e-mail: Lester.D.Thompson@kp.org

J. T. Braun
Department of Pathology, Maryland General Hospital, Baltimore, MD, USA

M. Pennant
Department of Head and Neck Surgery, Maryland General Hospital, Baltimore, MD, USA

Published online: 24 December 2009

seem to be more frequently syndrome associated or familial, but less likely to be malignant [2].

Within the head and neck region, paragangliomas tend to develop at the bifurcation of the common carotid artery, in the middle ear and temporal bone, and only isolated cases within the orbit, nasal cavity, paranasal sinuses, larynx, trachea and thyroid gland [1, 3–5] There is only one previous case report of a paraganglioma arising within the parathyroid gland [6]. Needless to say, this is an astonishingly rare presentation of this neoplasm. The initial presenting symptoms are non-specific, making it difficult to render a definitive diagnosis preoperatively. This case report highlights the clinical, radiographic, histologic, immunophenotypic, and therapeutic approaches to primary parathyroid gland paraganglioma in the context of a case report and review of the literature.

Case Presentation

A 69 year old black woman presented with an enlarged, nodular goiter in the left lobe of the thyroid gland and a greater than 5 years history of hypothyroidism. She complained of fatigue, heat intolerance, increased sweating, palpitation, constipation, thinning of her hair and some difficulty swallowing. She denied flushing, headaches, worsening blood pressure, and cold intolerance. She had been on Synthroid for more than 5 years. An ultrasound demonstrated enlargement of the left lobe of the thyroid, and a retrosternal solid mass, interpreted to be in direct continuity of the thyroid lobe. A computed tomography scan showed nodular enlargement of the thyroid gland, with extension of the left lobe into the anterior mediastinum. There was no compression of the adjacent structures. The lower pole of the thyroid gland showed a complex nodule without microcalcifications or vascular alterations. An ultrasound guided fine needle aspiration was performed on the left thyroid gland complex nodule, which showed follicular epithelial cells and blood with the suggestion of intranuclear inclusions.

Past medical history included hypertension (150/80), heart disease (status post surgery 47 years ago for a ventricular-septal defect, repeated 17 years later due to failed closure), arthritis, cervical spondylosis, abdominal pain, and weight loss. Approximately 13 months before her presentation for the thyroid tumor, the patient had a right kidney clear cell renal cell carcinoma. The renal cell carcinoma was 1.3 cm, Fuhrman grade 2 of 4, and was limited to the kidney without any extension (AJCC Stage pT1a NX MX, Stage I). Her hypertension was managed with Lasix and hydrochlorothiazide. Intestinal metaplasia of the gastric mucosa was identified, as were separate foci of chronic gastritis, positive for *H. pylori* with a Dieterle stain. Specifically, she did not have any parathyroid gland disease clinically or radiographically, no adrenal masses, no additional paraganglioma, no pancreatic mass and no succinate dehydrogenase (*SDH*) gene mutation. Therefore, it is concluded this was an isolated finding without any other stigmata of Multiple Endocrine Neoplasia (MEN) or inherited syndromes.

A number of laboratory values were abnormal. Specifically, multiple serum calcium levels ranging from 8.5 up to 10.2 mg/dl (normal, 8.6–10.0 mg/dl), with one of them slightly above the normal; ionized calcium of 1.26 (normal, 1.15–1.29 mmol/l); and thyroid peroxidase autoantibodies of 4,907 U/ml (normal <60 U/ml). A number of other analytes were normal, obtained either pre- or immediately postoperatively, including alkaline phosphatase; PTH (parathyroid hormone: 43; normal, 12–88 pg/ml); metanephrines, epinephrine, norepinephrine, dopamine and aldosterone levels (serum and/or urine).

Physical exam showed a thyroid goiter, with slightly enlarged left lobe more than the right lobe. Otherwise, the physical examination was unremarkable. The patient had a left hemithyroidectomy and excision of the left substernal thyroid mass. During surgery, the mass in the substernal area was *not* attached to the thyroid gland. The left superior parathyroid gland was visualized and was interpreted to be normal. The lobe of the thyroid was removed without incident. The superior mediastinal mass was removed intact by blunt dissection.

The specimen had two parts. The $3 \times 2.1 \times 0.8$ cm thyroid left lobe had multiple nodules identified macroscopically. There were a number of non-encapsulated light pale nodules measuring up to 0.3 cm in greatest dimension. The second specimen (substernal mass), showed an egg-shaped mass measuring 3.2 cm in greatest dimension and weighing 8 g. The tissue was fleshy-gray to hemorrhagic with a lobular appearance. No capsule was noted. The specimens were entirely submitted.

The histology of the substernal mass showed a well encapsulated and defined parathyroid gland, within which was a neoplastic proliferation of nests of paraganglia cells (Fig. 1). There was an intimate blending between the parathyroid parenchyma and the paraganglia cells, although without a destructive growth (Fig. 2). At the periphery, the parathyroid gland parenchyma was unremarkable, showing the usual fat to parenchyma ratio appropriate for the patient's age. The neoplastic cells were arranged in a *zellballen* architecture, focally showing a alveolar distribution. The cells had ample, basophilic granular cytoplasm. The nuclei were generally round to oval with delicate to coarse granular nuclear chromatin (Fig. 3). There were focal areas of tumor cell spindling. While variable, the tumor nests were similar in size. There was a richly vascularized, focally fibrotic stroma noted between the cell nests. Mitotic

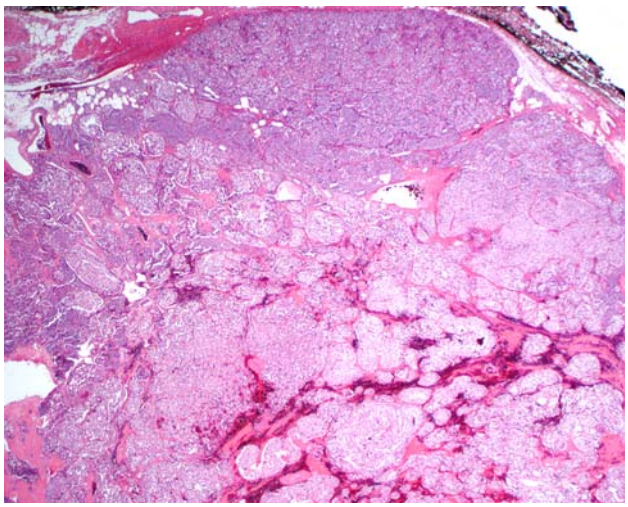

Fig. 1 The parathyroid gland at the *top* of the photograph has some parenchymal adipocytes. Within the milieu are multiple nests and zellballen associated with the parathyroid parenchymal cells

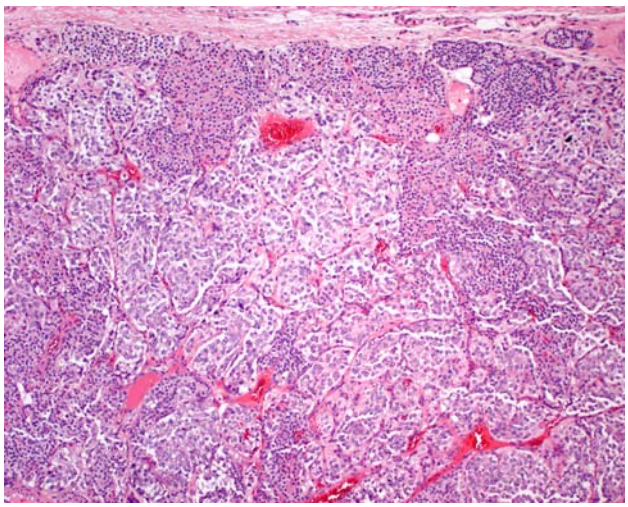

Fig. 2 There is a very intimate association of the paraganglia cells and the chief and oxyphilic cells of the native parathyroid gland tissue. Note the richly vascularized stroma

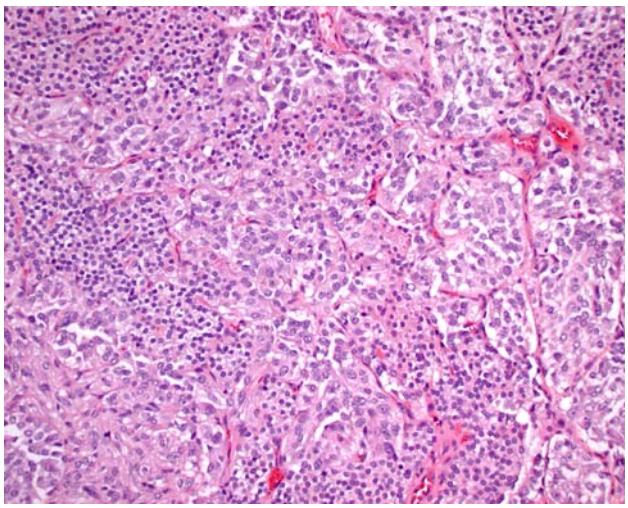

Fig. 3 This high power view illustrates a very close association between the paraganglia and islands of normal parathyroid parenchymal cells. The parathyroid cells are smaller with more hyperchromatic nuclei than the paraganglia cells

figures, necrosis, invasive growth, and profound nuclear pleomorphism were absent. The neoplastic cells were strongly and diffusely immunoreactive for chromogranin, synaptophysin, and CD56 (Fig. 4). A delicate, but well developed supporting sustentacular framework outlining each of these nests (Fig. 5) was highlighted by S-100 protein immunohistochemistry stain. The Ki-67 (MIB) showed $<2\%$ nuclear reactivity, while the cyclin D1 showed 3–5% nuclear reactivity. The keratin, EMA, CD10, parathyroid hormone, calcitonin and RCC markers were negative. The keratin and parathyroid hormone reactions highlighted the residual parathyroid gland parenchyma (Fig. 5). These findings support a diagnosis of a primary parathyroid gland paraganglioma.

The thyroid gland showed multiple adenomatoid nodules, a background of chronic lymphocytic thyroiditis and an unremarkable intrathyroidal parathyroid gland. There were three separate foci of thyroid papillary carcinoma, the largest tumor measuring 0.3 cm in greatest dimension. These were interpreted to be microscopic (incidental) papillary carcinomas, completely excised by the procedure.

During follow-up she has remained free of any paraganglia diseases (no metastatic or other primary paraganglioma identified), she does not have any documented stigmata of MEN, has had normal serum calcium and parathyroid hormone levels, and she has not developed metastatic disease from the renal cell carcinoma. Repeat computed tomography scans have shown no lymphadenopathy or recurrent disease. She is alive, without evidence of disease at last follow-up (12 months).

Epidemiology

Paragangliomas arise from collections of specialized paraganglia cells that are distributed throughout the body. Derived from neural crest, they are associated with chemoreception and baroreception, secreting various catecholamines in response to a variety of stimuli. Those in the head and neck are predominantly parasympathetic, seldom associated with symptoms, although usually presenting as a pulsatile mass within the carotid body or middle ear regions. Rarely, they are found in other anatomic sites. While paraganglioma of the thyroid gland, which are very

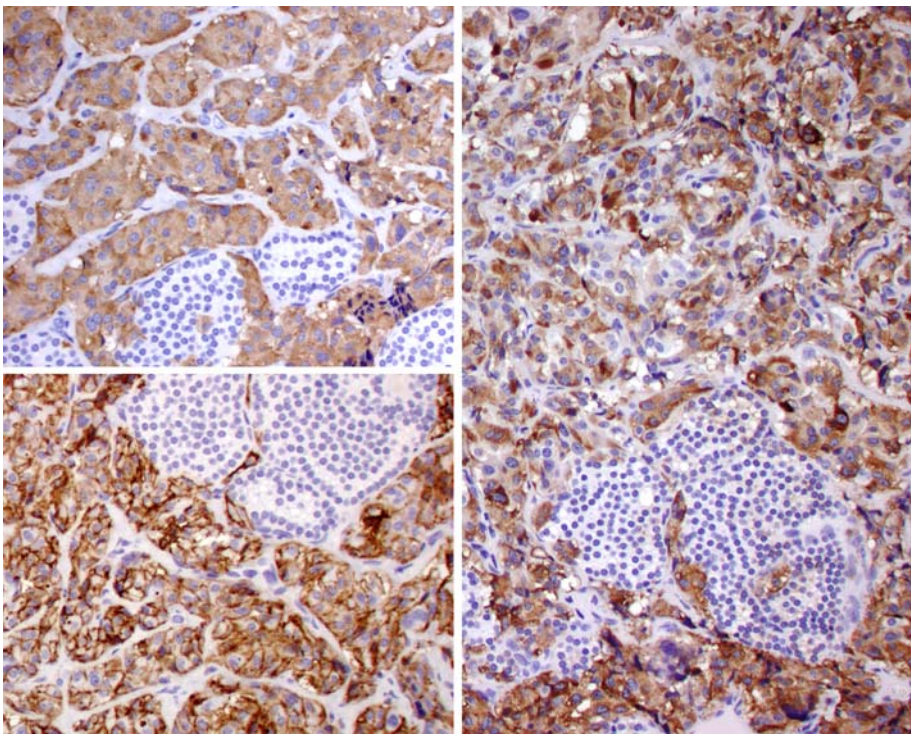

Fig. 4 This composite highlights the positive reactions in the paraganglioma cells in comparison to the negative parathyroid parenchymal cells. *Left upper* Synaptophysin in a delicate cytoplasmic reaction. *Left lower* CD56 shows a predominantly membranous reaction, although also positive in the cytoplasm. *Right* Chromogranin yields a strong and diffuse granular reaction in the cytoplasm

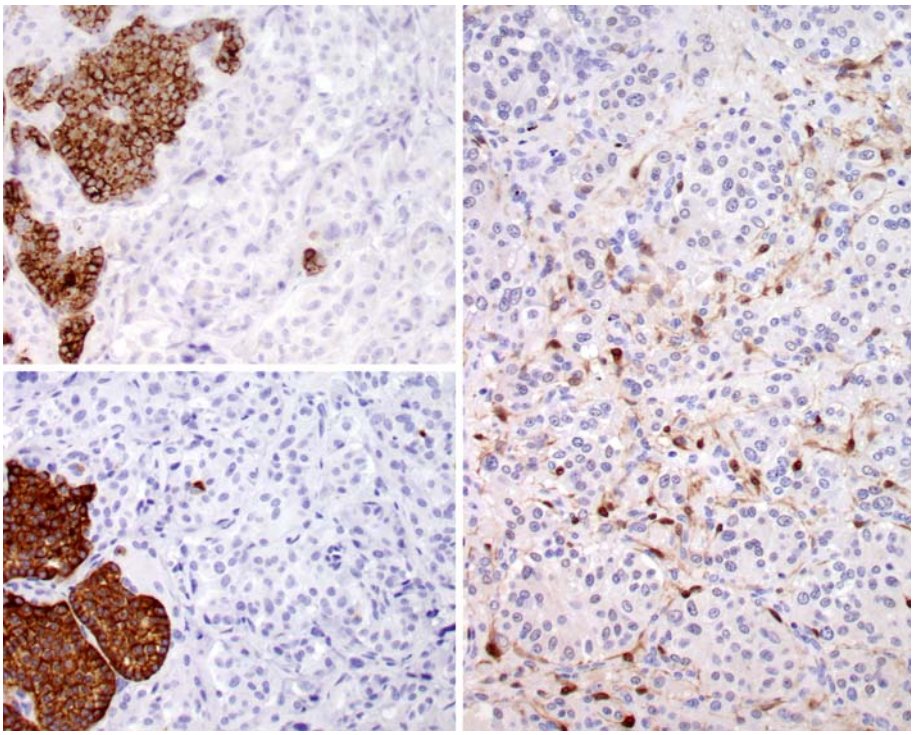

Fig. 5 *Left upper* Parathyroid hormone is strongly positive in the native parathyroid parenchyma, but negative in the paraganglia cells. *Left lower* The keratin stain yields an identical reaction pattern to the parathyroid hormone stain. *Right* The S-100 protein reaction shows a delicate, supporting sustentacular reaction around the paraganglia nests

rare, may arise from paraganglia within the thyroid gland capsule, [4, 5] paraganglioma of the parathyroid gland are more difficult to explain [6]. In this case, the parathyroid gland tissue was substernal. It is well known that parathyroid glands can be found anywhere along the route of normal embryologic descent, involving the 3rd and 4th branchial pouch apparatus. They can be identified within the thymus, mediastinum, and adjacent to the esophagus and great vessels. Therefore, the identification of paraganglia tissue within a parathyroid gland located in the mediastinum is interpreted to be developing within an "ectopic" although embryologic location. Interestingly,

there is a case report of ectopic parathyroid tissue identified within a neck paraganglion [7]. The preponderance of the tissue in this case was paraganglia, and so it could be argued it was parathyroid tissue entrapped within the paraganglia. However, the overall gland architecture was present, including areas of unremarkable parathyroid gland tissue with associated adipose tissue. Therefore, it is concluded, that although rare, parathyroid gland tissue and paraganglia can coincide. Further, both patients (ours and the case report) had tumors develop in the lower parathyroid glands, glands known to be more frequently associated with ectopic location. It may be that during embryologic development the lower parathyroid glands may be more prone to association with other developing structures in the region (thyroid gland, thymus, esophagus, trachea, and parathyroid glands).

There are isolated case reports of paraganglioma and hyperparathyroidism, in which there is a carotid body paraganglioma with a concurrent parathyroid adenoma [8, 9]. Further, there is a report of a cervical paraganglioma mimicking a parathyroid adenoma by ectopic secretion of parathyroid hormone, confirmed by immunohistochemistry [10]. Both paraganglia and parathyroid tissues are derived from neural crest, and both follow a sometimes similar anatomic development embryologically. Paraganglia can be intimately associated with parathyroid gland tissue.

Clinical Presentation and Associations

Both known patients have been elderly (66 years [6] and 69 years), although one male and one female (Table 1). Initially, both patients were clinically thought to have thyroid gland lesions, rather than parathyroid gland lesions. Both did not have significantly altered laboratory values. Most certainly a coincidence only, but both patients had a malignancy: a squamous cell carcinoma of the larynx with recurrence in pharynx [6] and a renal cell carcinoma. It could be hypothesized that the immune system is under challenge, allowing the paraganglia tissue to grow in the ectopic location.

Pathologic Features

Both cases show very similar histologic features, with an intimate blending of the paraganglioma cells with the parathyroid gland parenchyma. This is a unique feature, as

Table 1 Literature combined with current case [6]

Characteristic	Previous case	Current case
Reference	McCluggage [6]	Current case
Gender	Male	Female
Age (years)	66	69
Race	White	Black
Symptoms	Progressive dysphagia, weight loss	Enlarged, nodular thyroid gland with substernal extension; fatigue, heat intolerance, constipation
Duration	Not stated	60 Months (hypothyroidism)
Additional clinical findings	Recurrent squamous cell carcinoma (SCC) in posterior pharynx, mass in the right thyroid region	History of hypertension and heart disease; renal cell carcinoma without metastatic disease (13 months before)
Anatomic site	Inferior pole of the right lobe of the thyroid gland	Left anterior mediastinum, with extension into the lower neck
Physical exam	Right neck mass	Nodular enlargement of the thyroid gland without compression of adjacent structures (left > right)
Past medical history	Hemilaryngectomy for SCC of left larynx with neck dissection	Partial nephrectomy for renal cell carcinoma
Laboratory findings	Normal serum calcium	Slightly elevated serum calcium (10.2)
Size	2.5 cm	3.2 cm; 8 g
Histology	Paraganglioma within parathyroid gland showing compressed tissue at the periphery	Paraganglioma intimately associated with parathyroid gland tissue that was otherwise unremarkable
Immunohistochemistry	Positive: Chromogranin A, PGP 9.5; NSE Sustentacular: S100 protein positive Negative: Calcitonin, CAM5.2, CEAm, FVIIIR-Ag	Positive: chromogranin, synaptophysin, CD56; focal cyclin D1 and Ki-67; sustentacular S100 protein reaction Negative: keratin, EMA, CD10, parathyroid hormone, calcitonin, RCC
Treatment	Excision (parathyroidectomy, along with management for SCC)	Excision (part of the thyroid lobectomy)
Follow-up	Not stated	Alive, no evidence of disease (12 months)

paraganglioma normally present as a solid mass of paraganglion type nests. Therefore, it is a unique pattern. Since the parathyroid tissue is keratin positive, it can be difficult to separate the cell types, perhaps even raising the possibility of a carcinoid tumor. However, an S-100 protein would highlight the sustentacular cells. There is an overall lack of atypia, a lack of mitotic activity, and no necrosis. The "zellballen" or nested pattern is identified easily, highlighted by S-100 protein immunohistochemistry. The chromogranin, synaptophysin and CD56 are neuroendocrine markers, which can be positive in both the paraganglia cells as well as in parathyroid gland tissue. However, strong and intense staining with keratin and parathyroid hormone in the parathyroid parenchymal cells helps to separate the two populations. A lack of calcitonin helps to eliminate medullary thyroid carcinoma from consideration. The lack of EMA, CD10, and RCC help to exclude a metastatic renal cell carcinoma, an important consideration in the present patient who had a known history of clear cell renal cell carcinoma.

Differential Diagnosis

Differential diagnoses include an unusual parathyroid adenoma, metastatic paraganglioma to the parathyroid gland, medullary thyroid carcinoma, and metastatic clear cell carcinoma (such as renal cell carcinoma). A parathyroid adenoma tends to be a more uniform, encapsulated single cell-type proliferation within a fatless nodule. The paraganglia tissue in this case is uniformly distributed within the parathyroid parenchyma. Fat was present throughout and there was a lack of compression or atrophic parathyroid tissue. The lack of parathyroid hormone and keratin in the neoplastic cells would also help to exclude an unusual parathyroid adenoma.

With all neuroendocrine type tumors, it is difficult or neigh unto impossible to prospectively predict which tumors will develop metastatic deposits and show an aggressive biologic behavior. This is especially true of head and neck paragangliomas. It is well known that histologically benign appearing tumors can result in metastatic disease to lymph nodes and other distant, non-paraganglia affiliated anatomic sites. Therefore, the possibility of a metastatic (malignant) paraganglioma to the parathyroid gland must be considered. In this case, the strong and well developed S-100 protein sustentacular supporting framework suggests a more benign pattern of growth. Loss of S-100 protein has been associated with a more biologically aggressive clinical course for pheochromocytoma and paraganglioma [11]. Further, the lack of clinical and radiographic support for a paraganglioma in another location, lack of any significant mitotic activity, no lymphatic or vascular invasion, a lack of pleomorphism, and lack of necrosis militate against a metastatic deposit. There was a degree of monotony with a uniform cell size, suggesting a primary lesion. This patient had a history of clear cell renal cell carcinoma. However, the lack of keratin, CD10, EMA, and RCC, along with the positive neuroendocrine markers and sustentacular S-100 protein reaction removes a renal cell carcinoma from further consideration.

Based on the patient's age, it seems most unlikely that this is a forme fruste of a Multiple Endocrine Neoplasia (MEN) presentation. There are no clinical, laboratory, or radiographic findings to support such a consideration. Therefore, this tumor seemed to be an isolated finding. Interestingly, the patient has remained hypertensive, suggesting that the paraganglioma was not responsible for the patient's hypertension. It is difficult to posit management options, as both patients' tumors were "incidentally" discovered during evaluation for an unrelated disorder. Surgery seems prudent, with a specific clinical and/or radiographic evaluation suggested to exclude primary paraganglia elsewhere.

Conclusion

In conclusion, this report summarizes the findings of a primary, intraparathyroid gland paraganglioma. The tumor is exceedingly rare. It should be evaluated in the context of separating primary parathyroid tumors from a metastatic tumor versus a primary lesion in this site. Selected immunohistochemistry studies can help to make the distinction. Clinical exclusion of a paraganglioma in another site is probably wise, dependent on the age and other manifestations of the patient.

Acknowledgments The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Southern California Permanente Medical Group or Maryland General Hospital. There is no financial conflict of interest.

References

1. Lack EE, Cubilla AL, Woodruff JM. Paragangliomas of the head and neck region. A pathologic study of tumors from 71 patients. Hum Pathol. 1979;10:191–218.
2. Barnes EL, Tse LLY, Hunt JL, Michaels L. Tumours of the paraganglionic system: introduction. In: Barnes EL, Eveson JW, Reichart P, Sidransky D, editors. Pathology and genetics of head and neck tumours. 3rd ed. Lyon: IARC Press; 2005. p. 362–3.
3. Lack EE, Cubilla AL, Woodruff JM, Farr HW. Paragangliomas of the head and neck region: a clinical study of 69 patients. Cancer. 1977;39:397–409.
4. LaGuette J, Matias-Guiu X, Rosai J. Thyroid paraganglioma: a clinicopathologic and immunohistochemical study of three cases. Am J Surg Pathol. 1997;21:748–53.

5. Yano Y, Nagahama M, Sugino K, Ito K, Kameyama K, Ito K. Paraganglioma of the thyroid: report of a male case with ultrasonographic imagings, cytologic, histologic, and immunohistochemical features. Thyroid. 2007;17:575–8.
6. McCluggage WG, Cameron CH, Brooker D, O'Hara MD. Paraganglioma: an unusual tumour of the parathyroid gland. J Laryngol Otol. 1996;110:196–9.
7. Michal M. Ectopic parathyroid within a neck paraganglion. Histopathology. 1993;22:85–7.
8. Ali IM, Graham C, Sanalla B, Bell D. Carotid body tumor associated with hyperparathyroidism. Ann Vasc Surg. 1994;8:595–8.
9. Steely WM, Davies RS, Brigham RA. Carotid body tumor and hyperparathyroidism. A case report and review of the literature. Am Surg. 1987;53:337–8.
10. Bhattacharya A, Mittal BR, Bhansali A, Radotra BD, Behera A. Cervical paraganglioma mimicking a parathyroid adenoma on Tc-99 m sestamibi scintigraphy. Clin Nucl Med. 2006;31:234–6.
11. Thompson LD. Pheochromocytoma of the Adrenal gland Scaled Score (PASS) to separate benign from malignant neoplasms: a clinicopathologic and immunophenotypic study of 100 cases. Am J Surg Pathol. 2002;26:551–66.