Non-Functional Parathyroid Carcinoma: A Review of the Literature and Report of a Case Requiring Extensive Surgery

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Abstract  Parathyroid carcinoma is a rare malignancy, and only accounts for 0.5–2% of cases of primary hyperparathyroidism. Less than 10% of parathyroid carcinomas are non-functional, and as such, they have been rarely reported in the literature. Importantly, margin status at resection is related to prognosis, and only a handful of case reports of non-functional carcinoma note this important parameter. Here we report the first case of non-functional parathyroid carcinoma with negative margins, and review the literature on this rare entity. Whether functional or non-functional, parathyroid carcinoma can often be difficult to differentiate from benign parathyroid adenoma. While diagnosis has been based on clinical and histological criteria, recent data concerning the molecular underpinnings of parathyroid carcinoma may allow for improved accuracy in distinguishing benign and malignant parathyroid tumors.

Keywords  Parathyroid · Carcinoma · Non-functional · Parafibromin

Clinical Features of Parathyroid Carcinoma

Parathyroid carcinoma is the least common endocrine malignancy, and accounted for only 0.005% of cases reported to the National Cancer Database (NCDB) between 1985 and 1995 [1]. Roughly half of cases are diagnosed between ages 45 and 60 years, but the tumor arises over a wide age range. In the NCDB case series, overall 5- and 10-year survival rates were 85.5 and 49.5%, respectively. Most patients (>90%) present with symptoms of hyperparathyroidism, including severe hypercalcemia, an elevated serum parathyroid hormone (PTH) level, nephrolithiasis or nephrocalcinosis, osteopenia, gastrointestinal disturbances, depression, fatigue, or memory disturbance. Despite this, parathyroid carcinoma remains a rare cause of primary hyperparathyroidism, accounting for only 0.5–2% of cases. In comparison, benign parathyroid adenomas account for approximately 85% of cases, with diffuse hyperplasia comprising the remainder. Parathyroid carcinoma has been associated with hyperparathyroidism-jaw tumor (HPT-JT) syndrome, familial isolated primary hyperparathyroidism, and multiple endocrine neoplasia syndromes (MEN-1 and MEN-2A); patients with HPT-JT have a 15% prevalence of the tumor [2].

The management of parathyroid carcinoma is primarily surgical, with en bloc resection of the tumor with involved adjacent structures being the recommended primary mode of therapy. Indeed, at least one report indicates that survival is largely dependent on margin status of the primary resection [3]. There has been a long debate in the literature about the effectiveness of adjuvant therapy, largely fueled by the paucity of cases. However, three recent reports suggest that adjuvant radiation therapy may reduce tumor recurrence after resection [3–5]. There is no systematic data to suggest a role for adjuvant chemotherapy. Despite therapy, between one-third and three-quarters of patients have recurrence or metastasis of their tumors, causing recurrent hyperparathyroidism. Re-resection is the accepted therapy for palliative control of hypercalcemia, but seems to become less effective with continued iterations [6]. Calcimimetic agents, such as cinacalcet, have recently been used with success in the cases of primary hyperparathyroidism [7], and may also play a role in palliative management of
inoperable parathyroid carcinoma. Despite this, most patients who die of disease do so as a result of complications of hypercalcemia.

While functional parathyroid carcinoma is an uncommon tumor, non-functional parathyroid carcinoma is an exceedingly rare disease, with less than 20 reported cases in the last 80 years. As the name implies, patients with non-functional tumors have normal serum calcium and PTH levels, and do not present with symptoms of hypercalcemia. They typically present with a neck mass, and patients who die of disease eventually succumb to systemic tumor burden. Here we report a recent case of non-functional parathyroid carcinoma from our institution necessitating extensive surgery to obtain negative margins, review the past literature on this rare entity, and discuss recent and new advances in the diagnosis of both functional and non-functional parathyroid carcinomas.

Case Summary

The patient is a 59-year-old white man who presented to his primary care physician in July 2008 with a chief complaint of dysphagia. His past medical history was notable for diabetes mellitus type II, hypertension, and obstructive sleep apnea. Medications included metformin and amlodipine. He had previously undergone cervical spine surgery in 2002, and shoulder surgery at an unknown time. His family history was notable for a half-sister with a history of breast and gastric cancer, and an uncle with a history of an unknown head and neck cancer. He is married and works as a mechanic, rarely used alcohol, and had previously smoked cigarettes but quit in 1975.

On review of systems, he endorsed dysphagia and hoarseness, but denied other symptoms. Physical examination showed a 6-cm firm mass in the left neck. The mass extended anteriorly to the left sternocleidomastoid and inferiorly below the clavicle. Computed tomography, performed at an outside hospital in July 2008, was interpreted as a 6-cm left thyroid mass. The patient was subsequently referred to Barnes-Jewish Hospital for fine-needle aspiration of the mass, and evaluation by an otolaryngologist.

Under ultrasonographic guidance, a fine-needle aspiration of the presumed left thyroid lobe tumor was performed by radiology. A diagnosis of positive for thyroid carcinoma was returned at the end of July 2008, with a comment that the cytologic features raised the possibility of a poorly differentiated or insular variant of thyroid carcinoma; the cytologic differential diagnosis at that time included follicular variant of papillary thyroid carcinoma (Fig. 1). On the basis of findings, excision for examining tissue architecture was highly recommended.

He was then examined by one of our head and neck surgeons, who was concerned that the physical and radiographic characteristics of the tumor seemed more aggressive than that seen in the types of thyroid carcinoma given in the cytologic differential diagnosis. Indeed, magnetic resonance imaging of the mass, performed at Barnes-Jewish Hospital in early August 2008, showed a large left cervical mass that displaced the trachea to the right, extended between the trachea and esophagus in the neck, and inferiorly into the superior mediastinum (Fig. 2). Also at that time, the patient underwent an unremarkable laboratory work-up. Of note, the serum calcium was 10.1 mg/dl (nl = 8.6–10.3 mg/dl), and a serum thyroid function panel, including thyroid-stimulating hormone, triiodothyronine, thyroxine, thyroglobulin, anti-thyroglobulin antibody, and calcitonin, was within normal limits. In light of these incongruous findings, the patient was scheduled for a needle biopsy of the tumor prior to further management.

As in the prior cytology specimen, the needle biopsy showed a poorly differentiated tumor with morphological and immunohistochemical features suggestive of neuroendocrine differentiation (Fig. 3; see section Pathologic summary). The diagnosis was initially reported as poorly differentiated carcinoma with neuroendocrine features; the differential diagnosis included poorly differentiated/insular thyroid carcinoma, medullary carcinoma, parathyroid carcinoma, carcinoma with thymus-like elements, and neuroendocrine carcinoma. The common types of thyroid

Fig. 1 Fine-needle aspirate smears of non-functional parathyroid carcinoma (600×).

(a) Ethanol-fixed, Papanicolaou stained preparation; (b) air-dried, Diff-Quik stained preparation
carcinoma (papillary and follicular), as well as anaplastic carcinoma, were ruled out. A subsequent immunostain for PTH showed diffuse reactivity in tumor cells, and a diagnosis of parathyroid carcinoma was rendered. The patient had no symptoms of hyperparathyroidism, and a serum intact PTH was 20 pg/ml (nl = 14–72 pg/ml). He was scheduled for en bloc resection of a non-functional parathyroid carcinoma at the beginning of September 2008.

At operation, a large left cervical tumor was found, intimately involved with the left thyroid lobe. Dissection of the anterior pretracheal tissues showed tumor adhesion to the anterior trachea; frozen section analysis of this material was reported as “Rare atypical cells; recommend additional tissue.” Dissection of the tumor proceeded posteriorly from this point to the tracheoesophageal groove, where it appeared to invade the trachea and esophagus. At that point, it was deemed impossible to completely resect the tumor without sacrificing these structures. Eventually, the tumor was resected en bloc with the left thyroid lobe and isthmus, anterior cervical soft tissue, larynx, hypopharynx, superior esophagus, and first eight tracheal rings. A completion esophagectomy was performed, a gastric conduit

**Fig. 2** Pre-operative magnetic resonance imaging of non-functional parathyroid carcinoma. **a** T2-weighed transverse section, with carcinoma (arrowhead) displacing the trachea (single arrow) and compressing the esophagus (double arrow); **b** THRIVE sequence frontal section, with carcinoma extending across the midline and into the superior mediastinum.

**Fig. 3** Needle core biopsy of non-functional parathyroid carcinoma. **a–c** Hematoxylin and eosin-stained sections at **a** low (20×), **b** intermediate (100×), and **c** high magnification (600×). **d–f** representative high-magnification images (600×) of immunohistochemical stains for **d** cytokeratin AE1/AE3, **e** CD56, and **f** PTH.
was brought up to re-establish continuity, and a jejunostomy tube was placed for feeding. Portions of the manubrium, left clavicle, and left first rib were also excised to create access for a mediastinal tracheostomy.

Post-operatively, the patient was extubated and taken to the cardiothoracic intensive care unit, where he had a relatively uncomplicated course. He was able to transfer to an observation unit on post-operative day 2, and eventually to the floor. He was discharged from the hospital on post-operative day 18. After discharge, he was seen by our department of radiation oncology, and initiated adjuvant radiation therapy in mid-October 2008. This has been complicated by an episode of hemoptysis requiring inpatient observation about 1 month after initiating therapy. At the time of this report, the patient is approximately 7 months post-operative and has completed adjuvant radiotherapy. He tolerates oral intake and exercise, and has gained 5 pounds in the last few months. Although a computed tomogram of the chest performed February 20, 2009 showed two ill-defined “ground glass” opacities in the right and left upper lung lobes, he has no definitive evidence of tumor recurrence. His next scheduled clinical follow-up is at 9–10 months post-operative.

Pathologic Summary

Aspirate smears of the tumor (Fig. 1) were cellular and composed of crowded groups of tumor cells in a clean background. At high magnification, individual tumor cells showed round to oval nuclei, granular chromatin with occasional small nucleoli, and scant cytoplasm. The groups appeared cohesive and showed striking uniformity of size and shape.

The needle biopsy material (Fig. 3) showed solid nests of tumor cells separated by a dense fibrotic stroma, with tumor cells accounting for about one-quarter of the tissue examined. As in the cytology preparation, individual tumor cells were fairly uniform, with round to oval hyperchromatic nuclei, granular chromatin with inconspicuous nucleoli, and a small amount of eosinophilic cytoplasm. An extensive panel of immunohistochemical stains was performed to characterize the tumor. Tumor cells were strongly and diffusely reactive for cytokeratin AE1/AE3. They also showed weak or focal reactivity for the neuroendocrine markers synaptophysin, chromogranin A, and CD56. Stains for thyroglobulin, thyroid transcription factor-1, calcitonin, carcinoembryonic antigen, CD45/leukocyte common antigen, and CD5 were uniformly non-reactive. As previously mentioned, a subsequent send-out immunostain (Gen-Path; Cell Marque PTH antibody clone MRQ-29, prediluted; antigen retrieval with Ventana standard CC1 solution at 37°C for 32 min) showed diffuse and moderately strong staining for PTH, leading to the diagnosis of parathyroid carcinoma.

At operation, we received a composite en bloc resection of tumor and left thyroid lobe, larynx, superior trachea, hypopharynx, and superior esophagus (Figs. 4 and 5). The tumor and thyroid lobe was measured as 9.5 × 6.5 × 6.5 cm³. Gross sections of the specimen showed extension...
of a tongue of tumor into the tracheoesophageal groove, as suggested by pre-operative imaging (Fig. 2) and operative findings. Microscopic sections of the tumor again showed large solid nests of tumor cells separated by broad bands of dense fibrosis. At high magnification, tumor cells showed a crowded architecture, with focal areas of individual tumor cell necrosis. No large areas of geographic tumor necrosis were noted. Nests of tumor extensively involved the thyroid gland and anterior cervical soft tissues, with extensive lymphvascular space invasion. In addition, tumor cells extended through the membranous posterior trachea and approached the tracheal submucosal glands. Areas of the anterior trachea, near the area sampled by frozen section, also showed involvement by tumor. The tumor also involved the adventitia of the hypopharynx by direct extension. Although tumor approached the inked resection margins of the anterior cervical soft tissues, no tumor was seen at ink, and the sampled resection margins were free of tumor. A biopsy of the left recurrent laryngeal nerve submitted for frozen section analysis showed rare atypical cells, suspicious for carcinoma, only on the permanent sections. The separately received inferior esophagus and bones removed for tracheostomy access were free of tumor.

Non-Functional Parathyroid Carcinoma

Table 1 lists the 19 cases of non-functional parathyroid carcinoma reported in the literature since 1929, including the present case [8–26]. One case previously considered a non-functional carcinoma is in fact a non-functional recurrence of a primary functional parathyroid carcinoma [27] and so is not considered here. To summarize, most patients presented in the sixth or seventh decade with a neck mass, with an age range of 27 to 71 years. All patients were considered normocalcemic at the time of diagnosis, and had normal serum levels of PTH in cases where this was measured. Tumor size was variable, but almost half of the cases had tumors between 5 and 11 cm in size; in comparison, the NCDB case series reported a median tumor size of 3.3 cm [1]. All but one patient received surgical resection as the primary mode of therapy. The primary spread of tumor was locoregional invasion into the thyroid gland, cervical soft tissues, or superior mediastinum. Slightly over half of patients had recurrence of their tumors by the time of case report. Sixteen of 19 patients were alive at the time of case report, although most cases reported a relatively short follow-up period; only three of the cases have data beyond 5 years from the date of initial therapy.

More striking than the data presented in the above cases, however, is the data not reported. As noted in the section “Introduction,” the recommended mode of therapy for parathyroid carcinoma (both functional and non-functional) is en bloc resection of tumor with involved adjacent structures, and that overall survival directly correlates with the margin status of the initial resection [3]. Indeed, our present case report is the first non-functional parathyroid...
Table 1 Reported cases of non-functional parathyroid carcinoma

| Reference                                      | Age/sex | Clinical presentation                                      | Pre-operative Dx | Serum Ca (mg/dl) | Serum PTH (nl) | Tumor size (cm) | LN involvement |
|------------------------------------------------|---------|------------------------------------------------------------|------------------|------------------|----------------|-----------------|----------------|
| Current study                                  | 59/M    | Dysphagia, hoarseness, neck mass                           | Yes (IHC)        | 10.1 (nl 8.6-10.3) | 20 pg/mL (14-72) | 9.5x6.5 x6.5    | No             |
| Fernandez-Ranvier et al. [8]                   | 67/F    | Multinodular goiter                                        | No (MNG)         | 9.1              | 19 ng/dL (12-65) | 4.5x2 x0.8      | No             |
| Kirkby-Bott et al. [9]                         | 66/M    | Neck mass, tracheal obstruction                            | ?                | Normal           | ?              | ?               | ?              |
| Yamashita et al. [10]                          | 56/F    | Sore throat, neck mass                                     | No (thyroid adenoma) | 9.2         | Normal          | 3               | No             |
| Klink et al. [11]                              | 39/M    | Neck mass, hoarseness, nephrolithiasis                     | Yes (parathyroid scan) | 9.2          | 0.4 ng/mL (0.3-2.9) | 7.5x5.5 x5   | ?              |
| Collins et al. [12]                            | 65/M    | MNG, dyspnea, dysphagia                                    | No (MNG)         | 9.4              | ?              | 11 X5x5        | ?              |
| Murphy et al. [13]                             | 51/M    | Hoarseness, dyspnea, mediast. mass                         | No               | Normal           | Normal          | Extensive       | ?              |
| Merlano et al. [14]                            | 59/M    | Neck mass, VCP, dysphagia, axillary LN                     | No (adenoma with high Ml) | Normal     | Normal          | 8x6x4           | Yes            |
| Yamashita et al. [15]                          | 69/F    | Neck mass                                                  | No (thyroid carcinoma) | 9.3          | ?              | 5x4x3           | ?              |
| Hickey et al. [16–18]                          | 27/M    | Neck mass                                                  | No (cystic thyroid mass) | 9.2-9.8      | ?              | 5.5             | ?              |
| 49/M                                          | Neck mass | No                                                        | ?                | ?                | ?              | ?               | ?              |
| 59/M                                          | Neck mass | No                                                        | No (follicular thyroid ca) | 9.5          | ?              | 2.5             | Yes            |
| Chahinian et al. [19]                          | 69/F    | Neck mass, pleural effusion                                | No               | Normal           | Normal          | 2x2, 14         | ?              |
| Dhom and Hohbach [20]                          | 38/M    | Neck mass                                                  | No (thyroid nodule) | Normal         | ?              | 2.5x1.5         | ?              |
| Altenahr and Saeger [21]                       | 50/M    | Neck mass                                                  | No (thyroid tumor) | Normal         | ?              | ?               | Yes            |
| Pachter and Lattes [22]                        | 50/F    | Chest pain                                                 | No               | Normal           | ?              | Diffuse         | Yes            |
| Sieracki and Horn [23]                         | 43/F    | Neck mass, pain, dysphagk VCP                              | No               | 9.1              | ?              | 5x4             | ?              |
| McQuillan [24]                                 | 53/F    | Neck mass                                                  | No               | Normal           | ?              | ?               | Golf ball       |
| Armstrong [25]                                 | 71/F    | Neck mass                                                  | No (Hodgkin lymphoma) | 11.9         | ?              | 11x11 x4       | ?              |
| Guy [26]                                       | 29/F    | Neck mass, dysphagia, pain                                 | No (thyroid adenoma) | 8            | ?              | 8x6x4           | Yes            |

| Reference | Vascular invasion | Clear margins | Local invasion          | Local recurrence | Distant metastasis | Treatment (initial S) | Survival |
|-----------|-------------------|---------------|-------------------------|------------------|--------------------|-----------------------|----------|
| Current study | Yes           | Yes           | Yes (thyroid, trachea, hypopharynx) | No              | No                 | S + R (en bloc resection) | Alive at 7 months |
| Fernandez-Ranvier et al. [8] | Yes | ?              | Yes (thyroid) | Yes (neck, mediastinum) | Yes (lung) | S + R (total thyroidectomy) | Alive at 2 years and 7 months |
| Kirkby-Bott et al. [9] | ?            | ?              | Yes                     | Yes (neck)   | Yes (bone, lung)     | S + R (neck exploration, incomplete exc) | Dead at 8 years and 2 months |
| Yamashita et al. [10] | No            | ?              | Yes (thyroid) | No               | No                 | S + R (mass + thyroid lobe) | Alive at 10 months |
| Klink et al. [11] | Yes          | ?              | Yes (thyroid) | No                | No                 | S (en bloc resection) | Alive at 4 months |
| Collins et al. [12] | ?            | ?              | Yes (thyroid) | No                | No                 | S (L thyroid lobectomy) | Alive at 2 years |
| Murphy et al. [13] | Yes          | No             | Yes (mediastinum) | Yes (incomplete resection) | No | S + R + C (incomplete resection) | Alive at 11 months |
| Reference                  | Vascular invasion | Clear margins | Local invasion | Local recurrence | Distant metastasis | Treatment (initial S) | Survival                        |
|----------------------------|-------------------|---------------|----------------|-----------------|-------------------|----------------------|---------------------------------|
| Merlano et al. [14]        | ?                 | ?             | Yes (mediastinum) | Yes (mediastinum) | Yes (axillary LN, liver, supraclavicular LN) | Pre-operative R + S + R (biopsies) | Alive at 4 years |
| Yamashita et al. [15]      | ?                 | ?             | Yes (thyroid)   | No              | No                | S + R (completion L thyroid lobectomy) | Alive at 20 months |
| Hickey et al. [16–18]      | ?                 | ?             | Yes            | Yes              | Yes (axillary LN, lung, brain) | S + R + C (simple excision) | Dead at 2 years and 4 months |
|                            | ?                 | ?             | Yes (neck, mediastinum) | Yes (mediastinum) | Yes (lung, bone) | C                   | Alive at 9 months |
|                            | ?                 | ?             | Yes            | Yes (mediastinum) | Yes (lung, bone, LN) | S + C (total thyroidectomy, L radical neck dissection) | Dead at 1 years and 8 months |
| Chahinian et al. [19]      | ?                 | ?             | Yes (neck, mediastinum) | Yes (neck, mediastinum) | Yes (lung) | S + C | Alive at 8 years |
| Dhom and Hohbach [20]      | Yes               | ?             | Yes (thyroid)   | ?               | ?                | S (radical thyroidectomy) | ? |
| Altenähr and Saeger [21]   | ?                 | ?             | Yes (thyroid)   | Yes (neck)       | Yes (cervical LN) | S + R (L thyroid lobectomy) | Alive at 7 years |
| Pachter and Lattes [22]    | No                | ?             | Yes (mediastinum) | Yes (incomplete resection) | Yes (LN, skin) | S (partial excision) | Alive at 5 years |
| Sieracki and Horn [23]     | Yes               | ?             | Yes (neck, thyroid) | Suspicious (pericardium) | Suspicious (pantracheal LN) | S + R (subtotal resection) | Alive at 3 years |
| McQuillan [24]             | ?                 | ?             | Yes (thyroid)   | Yes (neck)       | No                | S + R (R thyroid lobectomy) | Alive at 2 years and 4 months |
| Armstrong [25]             | ?                 | ?             | Yes (neck, mediastinum) | No             | No                | S (en bloc resection) | Alive at 2 months |
| Guy [26]                   | ?                 | ?             | Yes (neck)      | Yes (lung)       | Yes (lung) | S + R (simple excision) | Alive at 2 years and 4 months |

An entry of ? Indicates that the information was not provided in the original case report.

IHC immunohistochemistry, MNG multinodular goiter, VCP vocal cord paralysis, MI mitotic index, Ca carcinoma, S surgery, R radiation therapy, C chemotherapy.
carcinoma to report negative margins after en bloc resection. Although most case reports do not comment on final margin status, we believe it is likely that many of these cases may have had tumor at or closely approaching the resection margins. This assumption is based on the fact that only 4 of the 19 patients received an en bloc or radical procedure as initial therapy. This may be due to current therapeutic practices at the time of resection. However, as listed in Table 1, only 2 of the 19 patients had a pre-operative diagnosis of parathyroid carcinoma; many more carried diagnoses that would not have indicated an extensive resection. If not definitely the case, it is likely that this diagnostic uncertainty also contributed to the surgical management of these patients.

To summarize, non-functional parathyroid carcinoma is a rare endocrine malignancy that presents with mass symptoms. Due to the paucity of cases and often limited clinical follow-up, it is difficult to compare survival to patients with functional parathyroid carcinoma. Non-functional parathyroid carcinoma is larger at presentation, appears to be best managed surgically, is often incompletely excised, and shows frequent locoregional recurrence and metastasis. It is likely that improvements in the accuracy of diagnosis will improve the management and outcomes for patients with both functional and non-functional carcinomas.

**Diagnosis of Parathyroid Carcinoma**

Clinically, a patient with primary hyperparathyroidism is most likely to have a parathyroid adenoma. Clues that the patient may have parathyroid carcinoma include a markedly elevated serum calcium (>14 mg/dl) or PTH (>5× the upper limit of normal), a palpable neck mass, or hoarseness (indicating involvement of the recurrent laryngeal nerve) [28]. Intraoperatively, a firm grey-white gland with adherence to, or invasion of, adjacent structures is suggestive of malignancy. Much like other endocrine malignancies, the gold standard for diagnosis of carcinoma is distant metastasis.

The histological criteria for the diagnosis of parathyroid carcinoma were published by Schantz and Castleman [29] in 1973, and are still valid today. They include: sheets or lobules of tumor cells separated by dense fibrous bands, mitotic figures, necrosis, capsular invasion, or vascular invasion. All of these features are seen in the present case. However, over 80% of parathyroid carcinomas are well-differentiated tumors [1], and some of these histologic features can be seen in atypical parathyroid adenomas [30]. Are there any other criteria to distinguish benign adenomas from their malignant counterparts?

Recent data have suggested that molecular testing may be useful in the cases of parathyroid tumors with equivocal histologic features. The first step in this process was the identification of HRPT2, located on chromosome 1q, as the gene mutated in HPT-JT [31]. Germline mutations were found in patients with HPT-JT, and sporadic mutations were also discovered in non-HPT-JT-associated parathyroid carcinomas. Additional studies also showed HRPT2 mutations in HPT-JT parathyroid adenomas and carcinomas, and sporadic carcinomas, suggesting that the gene may act as a tumor suppressor, and that its loss may be an initiating event in carcinogenesis [32, 33]. Expression of the gene product, termed parafibromin, has also been investigated in parathyroid neoplasia. Two studies suggest that sporadic adenomas show expression of parafibromin by immunohistochemistry, whereas most sporadic carcinomas and all HPT-JT-associated parathyroid tumors display loss of expression, in parallel with the gene mutation studies [34, 35]. The exact mechanism of carcinogenesis induced by the loss of parafibromin remains to be elucidated. Recent data suggest that the protein associates with RNA polymerase, regulates genes involved in cell growth and survival, acts as a cell cycle regulator, and plays a role in transducing transcriptional output from the Wnt pathway [36–40]. In addition to HRPT2, data also show that parathyroid carcinomas lose a greater proportion of tumor suppressor alleles as compared to benign causes of primary hyperparathyroidism, indicating genomic instability [41]. Testing for loss of these markers may supplement HRPT2/parafibromin analysis for diagnosis of borderline parathyroid neoplasms. The status of HRPT2/parafibromin in non-functional parathyroid carcinomas has not been investigated.

**Summary**

Parathyroid carcinoma is a rare cause of primary hyperparathyroidism, and <20 cases of it have been reported in the literature. In this study, we have reported the first case of non-functional parathyroid carcinoma with negative surgical margins after en bloc resection. Diagnosis of parathyroid carcinoma, whether functional or non-functional, is based on a number of clinical and histological criteria but can be challenging to differentiate from benign adenoma in many cases. In addition to traditional criteria, new advances in molecular diagnosis, including evaluation of HRPT2/parafibromin, may aid in improving diagnostic accuracy.

**Acknowledgments** We thank Dr. Rebecca Chernock for help with processing of the gross resection specimen, Dr. Samir El-Mofty and
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