Parathyroid Carcinoma Management in an Underdeveloped Country: A Case Series

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Abstract

Parathyroid carcinoma (PC) is a rare type of cancer that presents in individuals during their 4th or 5th decade of life; most cases are sporadic and of unknown etiology [1]. Approximately 1-2% of cases of hyperparathyroidism are caused by PC; with the average serum calcium levels higher in patients with PC than parathyroid adenomas (15.9 vs 12 mg/dL). Clinical diagnosis is often difficult and almost always invariably obtained after postoperative histopathological confirmation; making this disease rare and likely under diagnosed. Para fibromin immunostaining is currently the gold standard for definitive diagnosis; albeit its availability may be limited in resource-poor settings. We report a case series of five PCs who were diagnosed with primary hyperparathyroidism (pHPT) and underwent parathyroidectomy in a 10-year period. All of the patients in this case series presented post-surgery hungry bone syndrome (HBS). Efforts should be taken to establish more reliable and precise diagnostic tools to establish concrete guidelines for the management of PCs.

Keywords

Parathyroid carcinoma, Parathyroidectomy, Hyperparathyroidism, Hypercalcemia

Introduction

Parathyroid Carcinoma (PC) is an exceedingly rare malignancy and its prognosis is highly variable [2]. It has an incidence of approximately 0.5-5% in patients with primary hyperparathyroidism (PHPT), as parathyroid adenoma is the most common cause of hyperthyroidism in 87% -91% of all cases [3]. The 5-year survival rate ranges from 20% -85% [4]. Despite low mortality, PC is accompanied by serious clinical manifestations, in contrast with its benign counterpart parathyroid adenoma [4-5]. Most of these tumors are sporadic, although patients with Hyperparathyroidism-jaw tumor syndrome (HPT-JT), and multiple endocrine neoplasia (MEN) types 1 and 2A, have a higher risk of developing PC, ranging from 15% to 37.5% in different case series [2].

Parathyroid Carcinoma is a rare type of cancer that could present in individuals during their 4th or 5th decade of life. The clinical diagnosis of PC is often difficult and is almost always obtained only after a postoperative histopathological examination [1]. The real incidence of PC is difficult to establish, due to variable diagnostic criteria. Its histological features are not specific, as they have also been found in adenomas or even local recurrences of benign tumors [6] For this reason, the tumor’s malignancy must be unequivocally confirmed only after prolonged follow-up, bearing in mind both histological (capsular and vascular invasion) and clinical features (invasive appearance, recurrences, distal metastasis) [1,6]. Parafibromin immunostaining is currently the gold standard for definitive diagnosis. We report a case series

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of five PC, which presented with malignancies such as co-
synchronous Papillary Thyroid Carcinoma in one of the cases
and double adenomas in another, who were surgically treated
by the same surgeon. The American Association of Endocrine
Surgeons guidelines recommend patients with functional
PC should undergo regular surveillance by testing serum
calcium and PTH levels; however timeframe for follow-up is
not specified due to rarity of this under diagnosed malignancy
and drive by expert opinion [7]. Furthermore, there are no
available guidelines in Dominican
Republic for follow up of Parathyroid Carcinoma - especially
at 5-10-years periods, the primary surgeon in conjunction with
the Endocrine team had at least 1-10 years follow-up period,
with serum calcium, PTH control and ultrasound imaging.

Methods

A consecutive case series study was done in a single,
tertiary-level, university-based, referral center with a
retrospective data collection. The criteria of selection of these
cases included adult (age >18-years) patients who underwent
surgery having a diagnosis of pHPT. The data was extracted
from the patients in the Department of Endocrine Surgery of
CEDIMAT during study period January 2012 until December
2020. The exclusion criteria omitted patients diagnosed
with primary hyperparathyroidism at the expense of benign
parathyroid disease or that did not meet the pathological
criteria for PC. During this period of time a total of 69
parathyroidectomies were performed in this center. A total of
5 of these cases out of the 69 were found to have Parathyroid
Carcinoma (Table 1).

Consequently, this study was carried out in compliance
with international ethical regulations, including the relevant
aspects of the Declaration of Helsinki, and the guidelines
of the Council for International Organizations of Medical
Sciences (CIOMS). The study protocol and the instruments
designed were approved by CEDIMAT’s Institutional Review
Board (IRB); each patient, additionally, provided informed
written consent.

Preoperative laboratory assessments included a PTH test,
measurement of calcium serum and phosphorus, alkaline
phosphatase, 24h urine calcium, glomerular filtration rate (GFR),
and bone densitometry. Neck ultrasound and gammagraphy
studies were done to verify the location and existence of an
abnormal parathyroid gland. All patients underwent thyroid
pathology screening before undergoing surgery.

Preoperative PTH measurements were taken before
resection, and repeated 10 minutes intra-operatively after
resection of the tumor in all patients, confirming in all cases
a descent of more than 50%. Calcium levels were measured
24 hours after the surgery as part of standardized protocol
follow-up for downtrend of levels back to normal. The
extracted gland was then sent for frozen histopathology and
immunohistochemistry studies.

In these case series, all diagnosis confirmations were
histopathological and validated by immunohistochemistry
studies. Diagnostic pathology was confirmed by two
pathologists concurrence. One of them is from our center
(CEDIMAT), the other one from a Molecular Oncopathology
Laboratory in the U.S., validating the diagnosis via
immunochemistry studies. The markers used to confirm the
diagnosis in this study included Pan Cytokeratin cocktail (PCK),
Antibody against PTH (PT Hab), K1-67, Proliferation marker,
Thyroglobulin, and Calcitonin. These are the normal ranges
in our institution taken in consideration for laboratory values:

**Case series**

**Case -1**

**Clinical Presentation:** A 54-year-old Hispanic female, with
a past medical history (PMH) of arterial hypertension (HTA),
chronic kidney disease with nephrolithiasis, type -2 diabetes
mellitus (T2DM), Peripheral Vascular Disease (PAD),
and osteoporosis, presented to surgical consultation for primary
hyperparathyroidism initially diagnosed in the setting of
osteoarthralgia.

**Biochemical workup:** Total serum calcium levels were
elevated with 13.4 mg/dL, BUN of 75.2 mg/dL, creatinine of
3.81 mg/dL, high phosphorus levels (5.0 mg/dL), as well as an
elevated intact PTH (2,182 pg/mL) and a 24h calcium in urine
91.3mg/day (Table A and Table B and Table C).

**Radiological workup:** Thyroid/Parathyroid ultrasound
and mammography with technetium 99m sestamibi revealed
increased parathyroid gland size and uptake, respectively, in
the inferior right pole (Figure 1).

![Figure 1: Lower right parathyroid gland demonstrating malignant macroscopic features.](image)

**Table 1:**

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Normal ranges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>8.4 - 10.2 mg/dL</td>
</tr>
<tr>
<td>PTH</td>
<td>14 - 65 pg/mL</td>
</tr>
<tr>
<td>Creatinine</td>
<td>Adult men, 0.74 - 1.35 mg/dL</td>
</tr>
<tr>
<td></td>
<td>Adult women 0.59 - 1.04 mg/dL</td>
</tr>
<tr>
<td>BUN</td>
<td>6 - 24 mg/dL</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>2.8 - 4.5 mg/dL</td>
</tr>
<tr>
<td>24 hours calcium in urine</td>
<td>100 - 300 mg/day</td>
</tr>
</tbody>
</table>

**Figure 1:** Lower right parathyroid gland demonstrating malignant macroscopic features.
Immediate post-surgical issues: Temporary dysphonia as well as severe hypocalcaemia (6 mg/dL) due to HBS, 6 days post-op.

Long-term follow-up: A year after the procedure, the patient presented at follow-up with no laboratory results abnormalities was detected.

Additional data: Figure 1

**Table C**: Serum PTH values.

**Surgical details**: During the surgery, the affected lower right parathyroid gland was identified, displaying malignant macroscopic features. The affected gland was adhered to the carotid sheath, as well as its surrounding tissues. The 5 cm tumor infiltrated the retro-clavicular and retrosternal structures which protruded into the thorax, and was attached to the right lower lobe of the thymus. A decision was made on-site to perform en-bloc parathyroidectomy along with ipsilateral hemithyroidectomy and dissection and emptying of zone IV and VI, due to suspected malignancy.

**Histopathology/Immunohistochemistry findings**: Cytologic atypia, dystrophic calcification was found including capsular and vascular invasion. Immunohistochemical studies results showed positive PTH and PCK antibodies.

**Immediate post-surgical issues**: Temporary dysphonia as well as severe hypocalcaemia (6 mg/dL) due to HBS, 6 days post-op.

**Long-term follow-up**: A year after the procedure, the patient presented at follow-up with no laboratory results abnormalities was detected.

**Additional data**: Figure 1

**Case -2**

**Clinical Presentation**: A 62-year-old Hispanic male, with a known PMH of acute kidney injury and depressed mood.

**Biochemical workup**: Elevated serum calcium levels were found with 13.9 mg/dL, and elevated intact PTH levels (160.9 pg/ml) (Table A and Table B and Table C).

**Radiological workup**: Mammography with technetium 99m sestamibi demonstrated an increased uptake activity adjacent to the left lower pole (Figure 2).

**Surgical details**: En-bloc resection of the affected parathyroid gland was conducted, along with ipsilateral hemithyroidectomy with lymph node dissection due to malignant suspicion during surgery.

**Histopathology/Immunohistochemistry findings**: Cytologic atypia as well as capsular and vascular invasion were found. Immunohistochemical studies results showed positive
**Case-3**

**Clinical Presentation:** A 72-year-old Hispanic female, with PMH of hypertension, arthritis, and osteoporosis, presented to surgical consultation due to a previous diagnosis of secondary hyperparathyroidism.

**Biochemical workup:** Preoperative laboratory test results revealed high calcium levels (12.1 mg/dL), elevated intact PTH levels (4,038 pg/mL), BUN of 75.2 mg/dL, creatinine of 3.81 mg/dL, and high phosphorus levels (3.5 mg/dL) (Table A and Table B and Table C).

**Radiological workup:** An ultrasound and gammagraphy revealed an abnormal lower right parathyroid gland and suspicious thyroid nodules (Figure 3A).

**Surgical details:** Fine needle aspiration (FNA) of a thyroid nodule revealed synchronous papillary carcinoma of the thyroid of category V Bethesda (Figure 3B). Histopathology/immunochemistry findings: Cytologic atypia and ischemia, FNA revealed synchronous papillary carcinoma of the thyroid of category V Bethesda (Figure 3B).

**Immediate post surgical issues:** Patient presented to outpatient clinic on day 7 post op for numbness. His labs were consistent with HBS.

**Long term follow-up:** By 11-months, follow-up laboratory work-up showed normal serum calcium levels at 9 mg/dL. At 8-year follow-up, no laboratory results abnormalities were detected.

**Additional data:** Figure 2

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**Case -4**

**Clinical Presentation:** A 58-year-old Hispanic female with PMH of osteoporosis, depression, and renal lithiasis, presented to consultation with lethargy. An initial diagnosis of primary hyperparathyroidism was made prior.

**Biochemical workup:** Preoperative laboratory test results revealed high calcium levels (12.3 mg/dL), elevated intact PTH levels (179 pg/mL), BUN of 75.2 mg/dL, creatinine of 3.81 mg/dL, and high phosphorus levels (3.5 mg/dL) (Table A and Table B and Table C).

**Radiological workup:** Gammagraphy assessment demonstrated increased uptake activity adjacent to both inferior poles (Figure 4).

**Surgical details:** An inferior bilateral en-bloc resection of the parathyroid gland was conducted. After biopsy findings...
revealed PC, reintervention with hemithyroidectomy and dissection and emptying of zone IV and VI was performed.

**Histopathology/Immunohistochemistry findings:** Cytologic atypia as well as capsular and vascular invasion was found in one of the affected parathyroid glands. Immunohistochemical studies results showed positive PTH and pan-cytokeratin antibodies and high proliferation index of KI-67, consistent with a diagnosis of PC.

**Immediate post surgical issues:** HBS

**Long term follow-up:** At 1 year follow-up, the patient demonstrated persistent increased PTH levels (290 pg/ml).

Additional data: Figure 4A and Figure 5B

**Discussion**

The most common symptoms among patients in our case series with this condition were as follows; bone pain, osteopenia, depressed mood, lethargy, kidney lesions, nephrolithiasis, and/or osteoporosis, consistent with severe hypercalcemia signs and symptoms presented in other studies regarding PC presentation [1]. According to recent studies, the average serum calcium level in patients with PC is higher

![Figure 4: Visual gammagraphy assessment of Technetium-99 m methoxy-isobutylisonitrile demonstrated an increase of MIBI uptake activity in bilateral inferior poles.](image1)

![Figure 5A: Preoperative visual gammagraphy assessment of Technetium-99 m methoxy-isobutylisonitrile demonstrated an increase of MIBI uptake activity right inferior parathyroid gland.](image2)

![Figure 5B: Lower right parathyroid gland demonstrating malignant macroscopic features.](image3)

All of the patients in this case series presented post-surgery HBS. HBS usually reflects rapid mineralization after correction of hyperparathyroidism, causing severe and prolonged hypocalcaemia. It’s a rare complication, however, it’s often seen after a parathyroidectomy due to hyperparathyroidism, and it’s relatively common after removal of a PC [11]. According to recent literature, the more severe the bone disease before surgery, the more prone the patient is to HBS after surgery [12]. Despite being an unfavorable outcome, the HBS state suggests that surgical removal of hypersecretory parathyroid tissue was accomplished [12]. In this study, HBS was observed in all of the patients, 4 of whom presented severe bone disease before surgery. Notably, all patients presented with relevant history of Chronic Kidney Disease. To the authors current knowledge, there are no have been no studies looking at association between Chronic Kidney Disease and development of Parathyroid Carcinoma (or vice-versa). PTH and Calcium values remained normal at 1-year follow-up in all cases.

Conclusion

Due to its low incidence, PC is considered an extremely rare tumor that continues to present many challenges in diagnosis, resulting in a more difficult presentation to treat. Despite this pathology being extremely rare, 5 cases were reported in this center in the past 10-years, out of 69 patients that underwent parathyroidectomy, for a rough estimate of 7.2% of all cases.

Diagnosis may be suspected when there is an extreme elevation of PTH and serum calcium levels, but can only be confirmed after histopathological and immunohistochemistry study after the tumor is resected. Due to the later years seemingly increased frequency of PC and in the absence of a gold standard test, a multidisciplinary approach, considering all clinical, biochemical, and structural aspects of the disease, offers the best chance for accurate diagnosis.

HBS should be expected in patients with severe hyperparathyroidism due to PC after correction with surgical resection of the affected gland. Efforts should be taken to establish more reliable and precise diagnostic tools to establish concrete guidelines for the management of PC.

References


