An Intraoperative Surprise: Occult Case of Non-Functional Parathyroid Carcinoma

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INTRODUCTION

Parathyroid carcinoma (PC) exists in <1% of patients with hyperparathyroidism (**Figure 1**) and typically presents with a robust constellation of findings that rarely go unnoticed. Mean serum parathyroid hormone (PTH) concentrations are commonly 3-to 10-fold higher than the upper limit of normal with a mean serum calcium concentration that frequently exceeds 14 mg/dL. PCs also tend to metastasize to cervical lymph nodes (30%) which is a distinctly ominous sign when associated with this rare pathology as compared to its benign counterpart, parathyroid adenomas. Non-functioning parathyroid carcinomas (NPC), less than 10% of PCs, are exceptionally rare, and can more closely resemble parathyroid adenoma/hyperplasia on preoperative workup further obscuring diagnosis. This disease represents a unique subset of PCs that are rarely addressed in the literature.

Causes of 1° Hyperparathyroidism

- Parathyroid adenoma (~ 85%)
- Parathyroid hyperplasia (~ 15%)
- Parathyroid carcinoma (< 1%)

Figure 1. Most common causes of Primary Hyperparathyroidism.
The sheer scarcity of parathyroid carcinoma poses a significant challenge in making the diagnosis preoperatively

CASE REPORT

Hospital Course: A 57-year-old male presented for surgical evaluation of primary hyperparathyroidism following a 2-year history of progressive fatigue, back/hip pain, difficulty with memory and concentration, and a history of nephrolithiasis. Sestamibi scan did not localize a mass, but ultrasound demonstrated a possible left, inferior, parathyroid adenoma. Preoperative labs are shown in **Figure 2** and supported a diagnosis of parathyroid adenoma versus hyperplasia. An enlarged, bland, left inferior parathyroid was resected. Continued dissection to identify the left superior parathyroid gland revealed a paratracheal mass housed within dense fibrous tissue and grossly adherent to the esophagus. Interestingly, frozen section analysis of the left inferior parathyroid was consistent with adenoma and adequate intraoperative PTH decline was obtained prior to removal of the paratracheal mass. Intraoperative biopsy (**Figure 3, 4**) of the mass was concerning for PC, prompting en bloc resection with the esophageal adventitia and outer musculature, ipsilateral thyroid lobectomy and central neck dissection.

Genetic Analysis: Genetic testing for familial isolated hyperparathyroidism-1 (FIHP, HRPT-1) included analysis of CDC73-related disorders encompassing the genes AP2S1, CASR, CDC73, CDKN1B, GNA11, MEN1, and RET, none of which demonstrated pathologic mutations.

Postoperative Course: The patient received 6000 centiGray of adjuvant radiation in 30 fractions over forty-two days starting four months after his procedure. Successful completion of his treatment course yielded no evidence of recurrence at 1-year post-treatment as confirmed by PET scan, CT scan, and 24-hour urine calcium. Long-term surveillance is planned for 24-hour urine calcium every year with neck ultrasound.

LAB VALUES

	Preoperative	Postoperative	2 mo Follow-up
Serum Ca^{2+}	**10.4** mg/dL (↑)	-	9.5 mg/dL
Serum Intact PTH	**77.6** pg/mL (↑)	32.2 pg/mL	30.3 pg/mL
Urine Ca^{2+} (24hr)	> **965** mg (↑↑)	-	**380** mg (↑)
25-OH Vitamin D	**25.0** ng/mL (↓)	-	35.0 ng/mL

Figure 2. Lab Values Throughout Patient Care.
Key lab values collecting at different points throughout care

HISTOLOGY

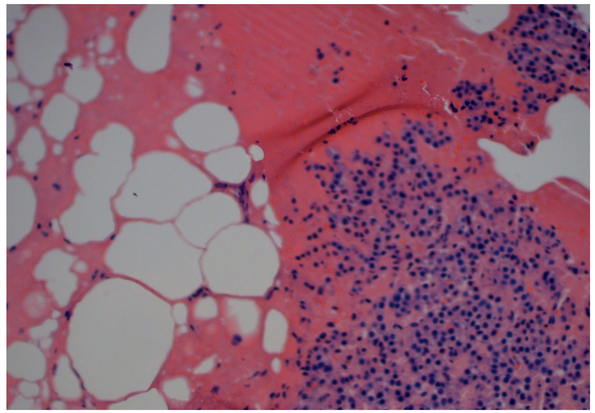

Figure 3.
Bland parathyroid carcinoma cells invading through the capsule into surrounding adipose tissue. H&E stained slide on 200X magnification

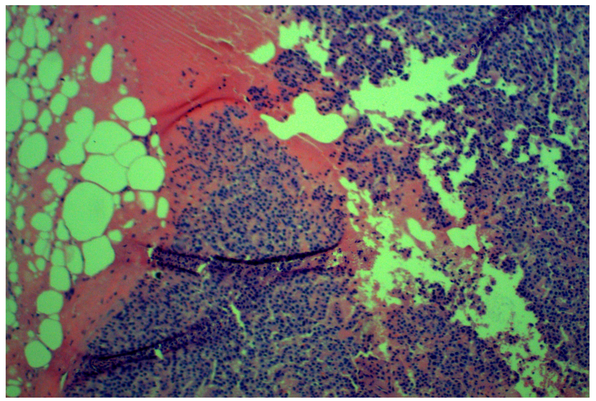

Figure 4.
Bland parathyroid carcinoma cells invading through the capsule into surrounding adipose tissue. H&E stained slide on 100X magnification

DISCUSSION

- PCs are the rarest endocrine malignancy worldwide and distinguishing them from parathyroid adenoma/hyperplasia can be challenging in the seldom encountered setting of mildly elevated lab abnormalities and absent neck masses.
- The intraoperative decline in the minimally elevated preoperative PTH (**Figure 2**) is especially fascinating and was arguably the first sign of an NPC because the carcinoma was still unresected when the PTH resulted. The gold standard for treatment is en bloc surgical resection of the tumor with any locally invaded tissue.
- Multidisciplinary tumor board recommended radiotherapy due to microscopic positive margin status.
- Postoperative evaluation is initiated with germline analysis of the tumor suppressor gene CDC73. Those found with mutations in CDC73, as well as, their next of kin, should undergo more stringent surveillance with 24-hour urine calcium or PTH levels every 6-12 months, in addition to, renal ultrasound and dental imaging every 5 years.
- Before committing to surveillance 24-urine calcium, our patient was evaluated for CYP24A1 mutation. This was done to minimize the risk of falsely elevated urinary calcium in the setting of a CYP24A1 mutation which would reduce the function of 24-hydroxylase, thereby increasing systemic active Vitamin D (calcitriol).
- Prognosis of PC is typically good following complete resection with 77 – 100% and 66 – 88% survival rates at 5- and 10-years, respectively; however, recurrences rates can be as high as 63% due to inaccurate preoperative PC diagnoses which result in inadequate oncologic resections.
- Prognosis of NPC is generally worse due to delayed diagnosis, frequent lymph node metastasis, and incorrect preoperative diagnosis, however, the literature surrounding this topic is lacking.
- Since NPCs are exceedingly rare, treatment and surveillance plans can be challenging.
- Currently, recommendations for this cancer are scarce, and increased descriptions of presentation, treatment, surveillance, and outcomes are necessary for adequate treatment of this rare disease.

CONCLUSIONS

- Parathyroid carcinomas can be non-secretory and early detection is crucial for optimal prognostic results.
- Intraoperative decline in elevated PTH despite an unresected parathyroid carcinoma can be the first sign of a non-functional parathyroid carcinoma.
- Adjuvant radiotherapy can be used in parathyroid carcinomas with microscopic positive margins to minimize recurrence at the 1-year mark.
- CYP24A1 mutations can result in falsely elevated urinary calcium and should be evaluated prior to developing a surveillance plan for parathyroid carcinoma.