Parathyroid Carcinoma Presenting as a Hyperparathyroid Crisis

To the Editor,

Although parathyroid carcinoma is a rare cause of hyperparathyroidism, it must be included in the differential diagnosis of parathyroid hormone (PTH)-mediated hypercalcemia and hyperparathyroid crisis, which is defined as a syndrome characterized by a serum calcium level > 14 mg/dL from a marked elevation of PTH, with severe signs and symptoms of hypercalcemia that are reversible with a correction of the hypercalcemia [1]. Imaging studies may be misleading; thus, careful attention to clinical features is important. Manifestations include mental status changes, nausea, vomiting, and abnormal cardiac and renal function. Given the recommendations against fine-needle aspiration biopsy (FNAB) of a suspected parathyroid carcinoma, the unique surgical approach to its treatment and the implications for family genetic counseling after diagnosis, parathyroid carcinoma must not be overlooked in cases of hyperparathyroid crisis.

We describe a 46-year-old male who was initially referred for renal failure and hypercalcemia. During the work-up, he underwent FNAB for a suspicious neck nodule, and was diagnosed postoperatively with parathyroid carcinoma. He has been cancer-free for 3 years following a left superior and inferior parathyroidectomy with an en bloc resection of the left thyroid and s/p external beam radiation therapy to the tumor bed and regional lymphatics.

Four weeks prior to transfer, the patient presented with fever, chills, severe myalgia, anorexia, nausea, dry cough, bilateral hand edema, arthralgia, muscle weakness, and pain in the prepatellar region of bilateral lower extremities. Routine blood tests revealed an elevated serum creatinine of 6.0 mg/dL, severe hypercalcemia (serum calcium of 17.42 mg/dL, corrected for albumin), elevated intact PTH (1,429.9 pg/mL), and low 1,25 vitamin D (7.8 pg/mL).

The patient’s medical history was significant only for mild to moderate ulcerative colitis. He had no history of irradiation to the neck, nephrolithiasis, or pancreatitis. Family history was unremarkable. The patient stated that he noticed rapid growth of an anterior neck mass over the past 4 weeks prior to admission.

A neck exam showed a 4 cm, hard, immobile mass in the anterior neck without lymphadenopathy. Heart, lung, and abdominal exams were unremarkable, other than sinus tachycardia. Edema of the proximal interphalangeal joints of bilateral hands without warmth or erythema was noted, and mild effusion and tenderness to palpation of bilateral infrapatellar regions was observed.

The patient was treated with aggressive rehydration via intravenous (IV) normal saline and subcutaneous calcitonin. On hospital day 9, the patient received one dose of 60 mg IV pamidronate.

A thyroid ultrasound showed a 3.3 × 4.2 cm heterogeneous mass in the left lobe of the thyroid with an internal cystic portion and a calcification segment in the periphery (Fig. 1A). This mass was suspected to be an indeterminate nodule, and FNAB was performed. The smear from the FNAB was consistent with a parathyroid proliferative lesion.

A chest computed tomography (CT) scan disclosed metastatic calcifications (calcium deposits in the lung interstitium) in both lungs and a soft tissue lesion in the left thyroid gland area, suspicious of parathyroid adenoma. A 18F-fludeoxyglucose positron emission tomography-CT scan (Fig. 1B) revealed a mildly hyper-
metabolic mass in the left thyroid area, suggestive of a benign tumor, such as parathyroid adenoma, and metastatic calcifications in the lungs, buttocks, and thighs. On hospital day 14, the patient received a left superior and inferior parathyroidectomy with en bloc resection of the left thyroid.

Histopathology revealed the left parathyroid mass to be a $4.5 \times 3.0 \times 2.0$ cm parathyroid carcinoma with focal vascular, capsular, and soft tissue invasion (Fig. 2A). No cancer involvement of the thyroid gland was found, and a negative resection margin was achieved. Immunohistochemistry was negative for p53 (1:400, Zymed, San Francisco, CA, USA), strong and diffusely positive for cyclin D1 (1:100, Novocastra, Newcastle, UK), focally positive for retinoblastoma protein (1:50, Novocastra), and positive for Ki-67 (1:200, Dako, Glostrup, Denmark) in 10% of tumor cells (Fig. 2B).

Given the evidence of capsular invasion on histopathology, adjuvant external beam radiation therapy was administered to the tumor bed and regional lymphatics.

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**Figure 1.** (A) Thyroid ultrasound showing a $3.3 \times 4.2$ cm heterogeneous mass. (B) A $^{18}$F-fludeoxyglucose positron emission tomography/computed tomography scan showing a mildly hypermetabolic mass in the left thyroid area.

**Figure 2.** (A) Gross surgical specimen shows a large parathyroid tumor with an irregular border and internal cystic components. (B) Histological appearance of parathyroid carcinoma, composed of neoplastic chief cells, showing infiltration into the tumor capsule and adjacent soft tissue (H&E, × 40).
On follow-up lung CT, the previously noted metastatic calcifications had markedly regressed. The 3-year follow-up thyroid ultrasound showed no recurrence of the tumor, and intact PTH was within normal limits.

In a series based on literature review of hyperparathyroid crisis from 1978-2007, Phitayakorn and McHenry [2] reported that the underlying parathyroid abnormality in 192 of 252 cases of hyperparathyroid crisis was parathyroid adenoma in 169 (88%), parathyroid carcinoma in 10 (5%), parathyroid hyperplasia in 10 (5%), and parathyroid cysts in five (3%).

It is important to distinguish between these causes of hyperparathyroidism prior to surgery because meticulous en bloc resection is the only chance for surgical cure of parathyroid cancer, whereas benign parathyroid conditions can be treated by adenomectomy or parathyroidectomy alone. Additionally, caution must be taken to prevent rupture of the tumor capsule in cases of parathyroid carcinoma; thus, FNAB should be avoided to decrease the chances of tumor seeding, subsequent local recurrence, and a worse outcome.

In a review article on parathyroid carcinoma by Shane [3], features that should raise the index of suspicion for parathyroid carcinoma rather than benign primary hyperparathyroidism include: male gender, younger age, serum calcium > 14 mg/dL, serum PTH 3-10 times the upper limit of normal, palpable neck mass, recurrent laryngeal nerve palsy, renal involvement, skeletal involvement, concomitant renal and skeletal disease, recurrent severe pancreatitis, peptic ulcer disease, anemia, and personal or family history of hereditary hyperparathyroidism-jaw tumor syndrome.

Since the report by Chow et al. [4] of the successful prevention of locoregional disease progression in patients with parathyroid cancer who underwent postoperative adjuvant radiation therapy, subsequent studies such as that by Clayman et al. [5] have also shown promising results. Adjuvant external beam irradiation was used in our patient to minimize the risk of local recurrence given the evidence of capsular invasion and penetration.

In conclusion, the differential diagnosis must include parathyroid carcinoma in patients presenting with hyperparathyroid crisis, and special care should be taken to avoid rupture of the tumor capsule either preoperatively during FNAB or intraoperatively. Although the most common cause of hyperparathyroid crisis is parathyroid adenoma, the index of suspicion for parathyroid carcinoma should be raised in patients with particularly elevated levels of PTH and calcium, a palpable neck mass, and concomitant bone and renal involvement. Aggressive en bloc removal of the affected parathyroid gland with ipsilateral thyroidectomy and isthmusectomy should be considered in these patients even if imaging suggests that the mass is benign, as this is the only chance for a surgical cure of parathyroid cancer. Adjuvant external beam radiation therapy may be added in select cases.

**Keywords:** Parathyroid neoplasms; Parathyroid cancer, adult; Hypercalcemia

**Conflict of interest**

No potential conflict of interest relevant to this article was reported.

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