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Hyperparathyroidism Presenting as Hypercalcemic Crisis

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Background	Hypercalcemic crisis is an infrequent presentation of primary hyperparathyroidism (PHPT).
Summary	A 60-year-old, previously active man presented to his local hospital with four weeks of severe fatigue. He was found to have a serum calcium level of 17 mg/dL, a parathyroid hormone (PTH) level of 1558 pg/mL, and mild renal insufficiency with serum creatinine of 2.4 mg/dL. He was diagnosed with hypercalcemic crisis in the setting of PHPT. He was treated with fluid repletion, intravenous bisphosphonates, calcitonin, and discharged home with a calcium of 11.1 mg/dL. Loop diuretics were not administered given his acute renal insufficiency. Neck ultrasound during his hospitalization demonstrated a 2.3 cm left inferior parathyroid adenoma, and a technetium-99 sestamibi scan co-localized to the left neck at the level of the inferior thyroid pole. He was urgently referred for surgical evaluation, and underwent parathyroid exploration 12 days after initial evaluation in the surgical clinic. Due to intraoperative concern for parathyroid carcinoma, the left lobe of the thyroid was resected with the enlarged parathyroid gland. Postoperatively, he did well, and his calcium level came down to 8.8 mg/dL. Final pathology demonstrated a 2.6 cm hypercellular parathyroid with decreased intracellular fat, consistent with parathyroid adenoma with no evidence of malignancy.
Conclusion	Hypercalcemic crisis due to PHPT is most commonly caused by parathyroid adenoma. The differential diagnosis also includes multi-gland parathyroid hyperplasia, parathyroid cyst, and rarely, parathyroid carcinoma. Initial treatment should focus on management of hypercalcemia via fluid repletion, judicious application of loop diuretics, intravenous bisphosphonates, calcitonin, and dialysis as a final resort. Surgical resection represents definitive management and should not be delayed.
Keywords	Hypercalcemia; hypercalcemic crisis; primary hyperparathyroidism; hyperparathyroidism; parathyroid adenoma; parathyroid cancer

Case Description

A 60-year-old, previously active man presented to his local hospital with four weeks of severe fatigue. In the year prior to presentation, he had declined from his baseline status as a full-time worker and marathon runner to having chronic fatigue, depression, and memory difficulties which prompted him to early retirement. Since his retirement, he found his fatigue worsening to the point where he was severely restricted in his daily activities.

On evaluation in the emergency department, he was found to be severely hypercalcemic, with a serum calcium level of 17 mg/dL (normal 8.5–10.5 mg/dL), a parathyroid hormone (PTH) level of 1558 pg/mL (normal 10–60 pg/mL), renal insufficiency with a serum creatinine 2.4

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mg/dL (normal 0.6–1.5 mg/dL), and a mild elevation in hepatic transaminases. No phosphorous level was available in the records received from his emergency department evaluation. One year prior to presentation, the patient had been noted to be hypercalcemic on routine laboratory evaluation, with a serum calcium level of 11.3 mg/dL, and a normal creatinine of 0.9 mg/dL and the patient denied any laboratory abnormalities prior to that time. No further evaluation of the hypercalcemia was pursued at that time. He had no history of nephrolithiasis, osteopenia or osteoporosis, or pathological fractures. His family history was notable for a sister with asymptomatic primary hyperparathyroidism (PHPT); the age of onset of PHPT in the sister was unknown, and she had elected not to have operative management.

The patient was diagnosed with hypercalcemic crisis in the setting of PHPT, and admitted to the hospital for further management. Per the report, his clinical examination was normal, without evidence of palpable, firm or fixed cervical mass, or cervical lymphadenopathy. He received fluid resuscitation, intravenous bisphosphonate treatment, and calcitonin to treat his hypercalcemia. Loop diuretics were not administered given his acute renal insufficiency. He was noted to have mild hypokalemia and hypomagnesemia, which responded well to oral supplementation. A 24-hour urine collection demonstrated elevated calcium excretion at 614 mg (normal 100–321 mg per 24 hours). At the end of a four-day admission, calcium levels had decreased to 11.1 mg/dL, creatinine had decreased to 1.9 mg/dL, serum transaminitis had resolved, and the patient's symptoms of fatigue had markedly improved. A DEXA scan performed during this hospitalization showed normal bone density. A neck ultrasound demonstrated a 2.3 cm nodule inferior to the left thyroid lobe, consistent with a parathyroid adenoma, without evidence of local invasion of the thyroid or other adjacent structures. A technetium-99m sestamibi scan showed focal uptake in the left lower neck (figure 1), co-localizing with the lesion noted on ultrasound.

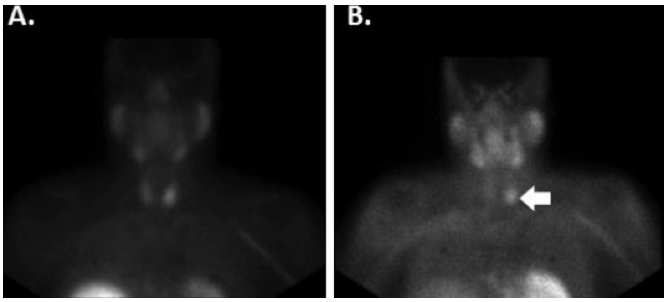

Figure 1. Anterior-posterior views of pre-operative technetium-99 sestamibi scan at 15 minutes (A.) and 2 hours (B.) after technetium administration, demonstrating marked uptake in the left lower neck (white arrow).

The patient was referred for urgent surgical evaluation, and was seen in the clinic less than 48 hours after hospital discharge. On presentation to the surgical clinic, his calcium level was 11.5 mg/dL, PTH was 1023 pg/mL, and creatinine 1.97 mg/dL. Preoperative discussion was held to consider the possible need for adjacent thyroid lobectomy in the event of intraoperative findings concerning for potential malignancy. An EKG was performed and was unremarkable; QTC intervals were normal. No EKG from his hospitalization for hypercalcemia was available for comparison. He was scheduled for parathyroid exploration expeditiously, and was taken to the operating room twelve days after initial evaluation in the surgical clinic.

Operative exploration was performed via a transverse cervical Kocher incision. On mobilization of the left thyroid lobe, an approximately 3 cm lesion was identified inferiolateral to the left thyroid (figure 2), corresponding to the lesion identified on ultrasound and sestamibi scan.

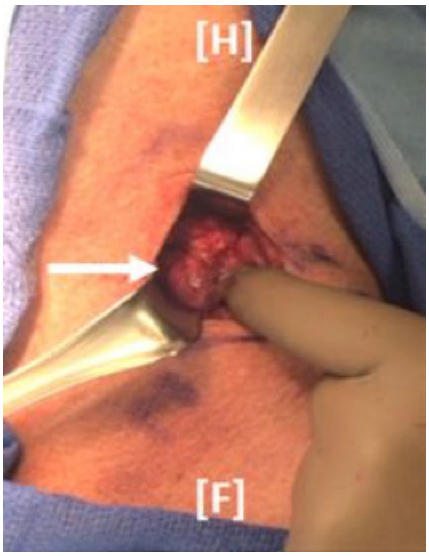

Figure 2. Operative exploration was performed via a Kocher incision. On retraction of the sternothyroid muscle, a lesion (white arrow) was noted lateral to the inferior pole of the left thyroid lobe.

The parathyroid tumor was abnormally adherent to the thyroid gland, but was not pale colored, firm, or fibrotic. Due to concern for possible rupture of the parathyroid tumor during the course of mobilization, as well as for the possibility of parathyroid carcinoma, the left lobe of the thyroid was resected with the enlarged parathyroid gland. The patient was admitted overnight for electrolyte monitoring due to his risk for hungry bone syndrome. Postoperatively, he did well, and was discharged home on 600 mg of elemental calcium three times daily, in addition to daily vitamin D3. His calcium levels decreased from 11.8 mg/dL immediately postoperatively to 9.9 mg/dL on postoperative day one, and then to 8.8 mg/dL on postoperative day three. Pathologic examination demonstrated a 2.6 cm hypercellular parathyroid with decreased intracellular fat (figure 3), consistent with parathyroid adenoma, with no evidence of malignancy.

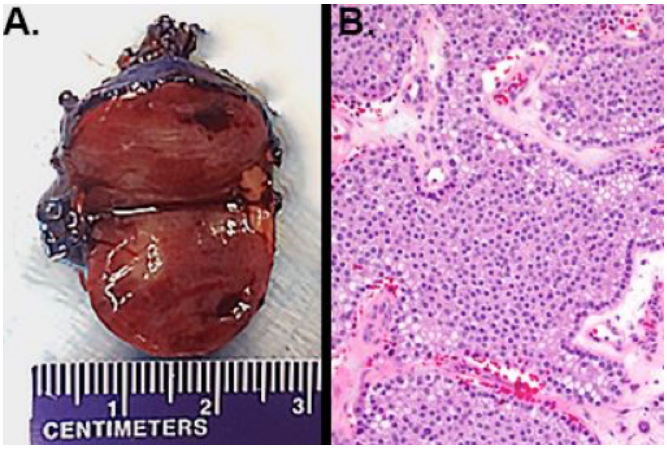

Figure 3. a) Gross pathology demonstrated a 2.6 cm parathyroid tumor. b) On hematoxylin and eosin staining, the parathyroid tumor was hypercellular, with decreased intracellular fat. No rim of normal parathyroid tissue was identified (200 X magnification).

Discussion

PHPT is the most common cause of hypercalcemia in the ambulatory population.[1] The incidence varies widely, from 0.4 to 21.6 cases per 100,000 adults annually.[2,3] Elderly females are two to three times more likely to be affected.[4] The causative entity of PHPT is most commonly a single parathyroid adenoma in 80%–85% of patients; multi-gland parathyroid disease constitutes a further 15% of cases, with parathyroid carcinoma contributing approximately 1% of cases.[5] Although PHPT is sporadic in >95% of cases, germline mutations in MEN1, and HRPT2 are associated with the familial PHPT syndromes of multiple endocrine neoplasia types 1 and 2A, and the hyperparathyroidism jaw-tumor syndrome, respectively.[6] In patients with familial syndromes, a higher suspicion for multi-gland disease may exist. Parathyroidectomy remains the only definitive therapy for PHPT, and bilateral exploration should be performed for patients in whom multi-gland disease is suspected.

Approximately 1.6%–6% of patients with PHPT present with hypercalcemic crisis.[7,8] Hypercalcemic crisis is variably defined as an adjusted serum calcium level of >13.5–14 mg/dL, with accompanying signs and symptoms of hypercalcemia.[8] Of PHPT patients presenting in hypercalcemic crisis, the underlying pathology is found to be parathyroid adenoma in 85%–88%; multi-gland disease in 5%–10%, parathyroid cyst in 0%–5%; and parathyroid carcinoma in 4.5%–5%.[8] Some authors suggest that a microcystic histologic pattern may correlate with hypercalcemic crisis in patients with parathyroid adenomas.[7] Treatment of hypercalcemic crisis includes intravenous fluid resuscitation, judicious use of loop diuretics once volume repletion has been achieved, bisphosphonates, and dialysis when other modalities fail.[8,9] Thiazide diuretics are contraindicated in the treatment of hypercalcemia, as they enhance calcium reabsorption in the distal tubule. With a rapid onset of action, calcitonin is a valuable adjunct to bisphosphonate therapy.[9] Once medical stabilization has been achieved, early surgery constitutes definitive management and is highly successful.[10,11] Traditional management consisted of emergency surgery within 24–72 hours; however this was associated with a high mortality rate.[12] Improved medical control of hypercalcemia with intravascular fluid repletion, bisphosphonates, and correction of electrolyte imbalances may stabilize patients for surgery and help prevent life-threatening arrhythmias.[8] The long lasting effects of bisphosphonates (2–12 weeks in the case of pamidronate) may contribute to the potential for postoperative hypocalcemia, underscoring the importance of close sequential monitoring after surgery.

Although hypercalcemic crisis raises clinical suspicion for parathyroid carcinoma, primary parathyroid malignancy remains an uncommon cause of hypercalcemic crisis.[13] Current guidelines of the American Association of Endocrine Surgeons suggest that a diagnosis of parathyroid carcinoma be considered in patients with primary hyperparathyroidism with markedly elevated serum calcium and PTH levels.[5] Although diagnosis of parathyroid carcinoma is made histologically, preoperative imaging demonstrating invasion of the thyroid or other adjacent structures might raise suspicion for carcinoma. No evidence-based guidelines exist for the preoperative evaluation of suspected

parathyroid carcinoma, but cross-sectional imaging such as CT or MRI might provide additional anatomic information in cases where sonographic evaluation is equivocal or suspicious. Intraoperative findings of a white or gray, firm, fixed, adherent or fibrotic mass would raise suspicion for a parathyroid carcinoma. Suggested operative management (if there is intraoperative suspicion for parathyroid carcinoma) includes complete resection of the parathyroid tumor with avoidance of capsular disruption, to prevent subsequent parathyromatosis. En bloc resection of adherent tissues, including adjacent thyroid gland, may improve the likelihood of cure if cancer is confirmed histologically.

Hungry bone syndrome is a postoperative complication encountered most commonly in patients with preexisting bone disease, and renal failure.[14] After parathyroidectomy, the abrupt decrease in PTH levels leads to a net influx of calcium, phosphate, and magnesium into bone, causing hungry bone syndrome. This manifests in electrolyte imbalances which may require frequent monitoring and intravenous repletion or dialysis to prevent neuromuscular and cardiac dysfunction.

Conclusion

PHPT is the most common cause of hypercalcemia in the nonhospitalized population. Hypercalcemic crisis is an uncommon presentation of PHPT. Although markedly elevated serum calcium and PTH levels raise clinical suspicion for parathyroid carcinoma, parathyroid adenoma remains the most common cause of both PHPT and PHPT presenting as hypercalcemic crisis. Mainstays of treatment of hypercalcemic crisis include intravenous fluids, induced calciuresis, bisphosphonates, calcitonin, and dialysis. Surgical resection remains the only definitive therapy for PHPT, and expeditious surgery after medical stabilization is recommended for patients presenting in hypercalcemic crisis.

Lessons Learned

Hypercalcemic crisis is an uncommon presentation of primary hyperparathyroidism. The differential diagnosis includes parathyroid adenoma, multi-gland hyperplasia, parathyroid cyst, and parathyroid carcinoma. Initial treatment should focus on management of hypercalcemia with fluid repletion, loop diuretics, intravenous bisphosphonates, and dialysis. Surgical resection represents definitive management, and should not be delayed.

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