Hypercalcemia in the Presence of an Ectopic Mediastinal Mass

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Abstract
A 72-year-old gentleman who presented to the outpatient clinic for a preventive health appointment with symptoms of depression and fatigue was found to have persistent hypercalcemia on routine laboratory monitoring. Initial laboratory testing was consistent with primary hyperparathyroidism with elevation in parathyroid hormone and low vitamin D levels. Further imaging demonstrated an ectopic mediastinal parathyroid adenoma. The ectopic lesion was treated surgically and lead to normalization of calcium levels and objective improvement in depressive symptoms. Primary hyperparathyroidism, which can be secondary to an adenoma, multigland hyperplasia, or neoplasm, can lead to the development of bone pain, fractures, and nephrolithiasis among other symptoms. The evaluation of hypercalcemia and the identification of primary hyperparathyroidism are important for the primary care physician to recognize so as to reduce disease morbidity as well as identify patients in need of further specialty care.

Keywords
primary care, community health, disease management, health outcomes, prevention

Case Presentation
A 72-year old man presented to the outpatient clinic for a routine preventive visit. The patient reported intermittent episodes of chronic low back pain, generalized fatigue, and depressive symptoms. A Patient Health Questionnaire (PHQ-9) depression scale revealed a score of 7/27 with concerns for decreased energy, lack of pleasure, and sleep difficulties.¹ His medical history was significant for type 2 diabetes (HbA1c of 8.3%), history of deep vein thrombosis/pulmonary embolism on warfarin, chronic low back pain secondary to spinal stenosis, epilepsy, obstructive sleep apnea, hypertension, gastroesophageal reflux disease, and depression. On completion of routine blood work, the patient was noted to have an elevated calcium level of 11.7 mg/dL (reference range: 8.8-10.2 mg/dL) with normal creatinine and electrolytes. Six weeks later, the patient’s calcium was once more elevated at 11.5 mg/dL. He reported no additional symptoms apart from those previously reported. Specifically, he noted no additional pain, gastrointestinal symptoms, or history of kidney stones.

On physical examination, the patient had a blood pressure of 133/73 mm Hg. His body mass index was 39 kg/m². His cardiovascular examination revealed a regular rhythm with 2/6 systolic murmur from a known sclerotic valve. His pulmonary, abdominal, and neurologic examinations were benign. His low back pain was worsened on lumbar extension with no red flags on examination.

Additional studies were obtained as reported in Table 1. Most notably, the patient’s parathyroid hormone (PTH) was significantly elevated at 130 pg/mL (reference range: 15-65 pg/mL) and 25-hydroxy D total was low at 11 ng/mL (optimal range of 20-50 ng/mL). A 24-hour urine calcium collection was performed, which demonstrated a urine calcium level >200 mg/d. A 24-hour urine creatinine collection was not obtained. The patient was advised to supplement with vitamin D, and given calcium level >1.0 mg/dL above the upper limit of normal, a sestamibi scan was performed, which demonstrated a focus of increased activity in the posterior mediastinum adjacent to the thoracic esophagus.

He was referred to Endocrinology and a computed tomography scan with contrast was obtained to further characterize the lesion which revealed a hypervascular lesion consistent with an ectopic parathyroid mass in the mediastinum. After evaluation by thoracic surgery, the patient

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underwent video-assisted thoracoscopic localization and removal of the mediastinal parathyroid adenoma. PTH 1 day after surgical removal was 21 pg/mL with a calcium level of 10.2 mg/dL. Four months later, the patient’s PTH was still within normal range at 61 pg/mL with a calcium level of 9.8 mg/dL. Repeat PHQ-9 6 months after surgery was improved at 0/27 and patient reported improvement in his fatigue.

### Discussion

Calcium homeostasis is a complex physiologic process that relies on the actions of PTH, calcitonin, and vitamin D metabolites. Through their actions on the bone, kidneys, and gastrointestinal tract, these hormones help regulate the level of calcium in the body. PTH is a polypeptide hormone secreted by the parathyroid glands that increases the amount of calcium in the extracellular fluid by increasing calcium resorption directly from the bone and increasing calcium reabsorption at the distal tubules of the kidney. PTH also stimulates the production of 1,25 dihydroxyvitamin D by the proximal tubules of the kidney, which increases calcium absorption in the intestines. PTH is regulated by a negative feedback loop with calcium and vitamin D, which suppress PTH secretion. Calcitonin, in contrast, reduces calcium levels primarily through its effect on osteoclast activity.²

Hypercalcemia is a disorder of calcium homeostasis with a heterogeneous group of etiologies. Primary hyperparathyroidism and cancer account for the majority of cases with primary hyperparathyroidism occurring most commonly in the ambulatory setting. Neoplasms, which may include parathyroid carcinoma or ectopic PTH in malignancy, are more common in hospitalized patients.³ Genetic causes such as familial hypocalciuric hypercalcemia or multiple endocrine neoplasia type 1 or 2 may produce hypercalcemia. Inflammatory or infectious causes such as sarcoidosis, tuberculosis, or inflammatory bowel disease may also lead to elevated calcium. Finally, endocrine pathology such as thyrotoxicosis or adrenal insufficiency as well as drugs such as thiazides and lithium can contribute.⁴

Today, hypercalcemia often presents as an incidental discovery on routine laboratory monitoring. As such, patients are often asymptomatic. Traditionally, patients with hypercalcemia would present with gastrointestinal discomfort, recurrent nephrolithiasis, bone pain, or neuropsychiatric symptoms. In patients with hypercalcemia, special attention should be paid to patient’s current medications, systemic symptoms such as weight loss that could indicate a possible underlying malignancy, the presence of a neck mass that could be concerning for a neoplasm, or any personal or family history of kidney stones, parathyroid, or pancreatic tumors.⁵

It is important to note that patients with calcium levels greater than 14 mg/dL (corrected for patient’s albumin level) require hospital admission. In these cases, intravenous hydration and administration of bisphosphonates are often warranted. Administration of calcitonin for rapid calcium reduction may also be utilized.⁴ In those not requiring hospitalization but with persistently elevated calcium levels, further laboratory studies should be performed starting with a PTH level (Table 2). In addition, vitamin D levels and creatinine should be obtained. A low PTH level raises concern for an ectopic source of PTH such as that from neoplasia, and a PTH–related protein (PTHrP) level should be measured. If the PTHrP level is normal or elevated, a neoplastic workup should commence.⁴,⁵ An elevated PTH level, often within 2 times the upper limit of normal, in the setting of hypercalcemia is consistent with a likely diagnosis of primary hyperparathyroidism.⁶,⁸ In patients with a normal or only minimally increased PTH level, a 24-hour urine collection should be obtained to calculate a calcium to creatinine ratio.⁴ Individuals with familial hypocalciuric hypercalcemia (FHH) typically have a ratio of <0.01 and require further familial workup and genetic testing. Primary hyperparathyroidism is the most likely etiology in patients with a calcium to creatinine ratio of >0.01.⁴,⁹

Although not required, a 24-hour urine calcium study may be utilized to differentiate FHH and primary hyperparathyroidism. Twenty-four-hour urinary calcium excretion in patients with FHH is usually less than 200 mg/d. Urine calcium levels greater than this are most consistent with primary hyperparathyroidism.¹⁰,¹¹ It is important to note that thiazide diuretics have been shown to decrease urinary calcium excretion and thus can interfere with interpretation of 24-hour urine calcium studies.¹² The patient described above was on hydrochlorothiazide; however, his urinary calcium level was >200 mg/d. Therefore, even in the presence of a drug that could reduce urinary calcium, his calcium level was most consistent with primary hyperparathyroidism.

After laboratory findings consistent with primary hyperparathyroidism are identified, occult manifestations of hypercalcemia should be investigated. Evidence of nephrolithiasis or nephrocalcinosis should be identified by plain

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**Table 1.** Laboratory and Imaging Studies.

| Test                      | Value                      |
|---------------------------|----------------------------|
| Creatinine                | 1.14 mg/dL (reference: 0.74-1.35 mg/dL) |
| Electrolytes              | Within normal limits       |
| Parathyroid hormone       | 130 pg/mL (reference: 15-65 pg/mL) |
| 25-hydroxy D total        | 11 ng/mL (reference: 20-50 ng/mL) |
| Phosphorus                | 1.6 mg/dL (reference: 2.5-4.5 mg/dL) |
| Urine 24-h calcium        | 214 mg (reference: <250 mg) |
| Renal X-ray               | No evidence of stones      |
| Bone density scan         |                            |
| Left hip: T score −1.4   |                            |
| Right hip: T score −0.6   |                            |
| Lumbar spine: T score −0.4|                            |
| Forearm: T score 0.7      |                            |
| No osteoporosis           |                            |

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2. 200 mg/d. Therefore, even in
radiograph imaging of the kidneys, ureters, and bladder. Investigation for bone mineral density (BMD) reduction should be completed via dual-energy X-ray absorptiometry (DXA) of the lumbar spine, hip, and forearm to evaluate for the presence of osteoporosis. Additional common laboratory findings in these patients include low serum phosphate, elevated alkaline phosphatase, and low levels of 25-hydroxyvitamin D.

A recent study demonstrated that the incidence of primary hyperparathyroidism in a racially diverse population in the United States was 25 per 100,000 person-years in men and 66 per 100,000 person-years in women with the highest incidence in the Black and Caucasian population. Furthermore, the incidence of hyperparathyroidism increased with advancing age.

Close to 80% of primary hyperparathyroidism cases are due to a single adenoma whereas approximately 15% are due to multigland hyperplasia. While some risk factors such as thiazide diuretics, lithium, and exposure to head and neck radiation at a young age have been noted in the literature, most cases of primary hyperparathyroidism are believed to occur sporadically.

Familial forms of primary hyperparathyroidism compromise up to 10% of cases due to mutations in MEN1, such as that found in multiple endocrine neoplasia type 1, and the RET gene in multiple endocrine neoplasia type 2A.

Classically, individuals with primary hyperparathyroidism could present with bone pain and proximal muscle weakness as well as bone fractures of the extremities. In these patients, X-ray imaging could also demonstrate pathognomonic findings consistent with primary hyperparathyroidism, including bone cysts, resorption of the distal phalanges, degranulation of the skull, tapering of the distal clavicle, and brown tumors—a collection of findings referred to as osteitis fibrosa cystica. Renal manifestations, including nephrolithiasis and nephrocalcinosis were also common and could lead to decreased renal function.

More recent studies have reported more subtle and nonspecific symptoms such as depression, anxiety, and difficulty concentrating in patients with primary hyperparathyroidism. While more subtle neuropsychiatric symptoms have been reported, the resolution of these symptoms after correction of hyperparathyroidism has not been consistently demonstrated.

The initial management of primary hyperparathyroidism is dependent on the presence or absence of symptoms. Symptomatic patients should undergo parathyroidectomy as surgery is the only curative treatment. As such, preoperative imaging is necessary for localizing the lesion for surgical planning and should be performed in collaboration with clinicians experienced in the treatment of primary hyperparathyroidism. The combination of cervical ultrasound as well as Technetium sestamibi scintigraphy can improve the accuracy of identifying lesions as well as increase sensitivity.

A majority of primary hyperparathyroidism cases are secondary to a single adenoma. Of these cases, it has been reported that 80% to 85% are located in their expected anatomical location next to the thyroid gland; however, 15% to 20% are located in ectopic locations. A retrospective study of patients at an academic center from 2000 until 2010 demonstrated that 22% of patients with hyperparathyroidism were secondary to ectopic parathyroid adenomas with 31% located in the retroesophageal region.

The location in the mediastinum presents an additional challenge due to increased difficulty with excision as many are not able to be excised using the typical cervical approach. Furthermore, due to the small size of ectopic mediastinal lesions, adequate localization prior to surgery is of utmost importance and scintigraphy is often necessary.

In asymptomatic patients, management of primary hyperparathyroidism is more nuanced and should be made with the assistance of an endocrinologist. According to the Fourth Workshop on the Management of Asymptomatic Primary Hyperparathyroidism, surgery is indicated in the following conditions: serum calcium >1.0 mg/dL above upper limit of normal, BMD with T-score <−2.5 at measured sites, creatinine clearance <60 mL/min, 24-hour urine calcium >400 mg/d and increased stone risk, presence of nephrolithiasis or nephrocalcinosis on imaging, and age <50 years.

Furthermore, any patient with a history of fragility fracture should have a parathyroidectomy. Genetic counseling should be offered to patients with evidence of primary hyperparathyroidism and multigland disease at less than 40 years of age or in the presence of a strong family history.

Surgical cure has demonstrated improvements in BMD as well as decreased risk of nephrolithiasis as compared to presurgical risk; however, no significant change has been appreciated in psychiatric symptoms. In patients who do not meet criteria for surgery, continued surveillance to determine whether they will meet surgical criteria is necessary.

### Table 2. Etiology of Hypercalcemia and Associated Laboratory Values.

|                          | Primary hyperparathyroidism | Malignancy | Familial hypocalciuric hypercalcemia |
|--------------------------|----------------------------|------------|------------------------------------|
| Parathyroid hormone      | Elevated (2× upper limit of normal) | Low/normal | Normal/mildly elevated              |
| Parathyroid hormone–related protein | Do not obtain | Normal/elevated | Normal/elevated                   |
| 24-h urine calcium       | >200 mg/d                  | Do not obtain | <200 mg/d                          |
| Urine Ca:creatinine ratio| >0.01                      | Do not obtain | <0.01                              |

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guidelines may be utilized. In these cases, the guidelines call for annual serum calcium levels, biennial DXA to determine if worsening BMD, and annual glomerular filtration rate.10

According to the American Association of Endocrine Surgeons Guidelines, continued monitoring after surgical intervention should include measurements of calcium, PTH, and 25-hydroxyvitamin D levels for at least 6 months. Many patients are discharged on vitamin D and calcium supplementation to combat secondary hyperparathyroidism due to vitamin D deficiency or inadequate calcium intake.8

In patients whose calcium level has returned back to baseline, routine PTH monitoring in the immediate postoperative setting is not recommended. However, PTH levels that have not returned to normal limits after 6 months can indicate failure of operative management.14

Above, we have described a case of hypercalcemia secondary to hyperparathyroidism due to an ectopic mediastinal mass. The patient reported neuropsychiatric symptoms of depression and fatigue; however, neuropsychiatric symptoms alone do not warrant recommendation for parathyroidectomy. However, the patient described did meet surgical criteria for asymptomatic patients given the presence of a calcium level >1.0 mg/dL above the upper limit of normal.10 While evidence for improvement in neuropsychiatric status after parathyroidectomy remains an active area of study and debate, it is important to note that the patient described did have objective improvement in both his PHQ-9 score as well as reports of fatigue 6 months after surgical management. This case, as well as other studies, demonstrates the need for continued research into the relationship between hyperparathyroidism and neuropsychiatric symptoms as well as what role, if any, surgical management could play in ameliorating these symptoms.

Conclusion

Given the prevalence of hypercalcemia and routine laboratory monitoring undertaken in primary care practices, the primary care physician should be comfortable with the clinical and laboratory evaluation of hypercalcemia. The above case describes hypercalcemia secondary to primary hyperparathyroidism due to the presence of an ectopic mediastinal mass. On removal of the patient’s parathyroid mass, his calcium and PTH level returned to normal levels, and he had improvement in his neuropsychiatric symptoms. This case demonstrates the rare occurrence of an ectopic mediastinal parathyroid mass as well as illustrates that resolution of hyperparathyroidism may lead to improvement in neuropsychiatric symptoms in patients with hypercalcemia. Prompt identification of primary hyperparathyroidism as well as appropriate management is important not only to reduce symptoms but to optimize a patient’s long-term bone and renal health.

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