CLINICAL VIGNETTE

The Tipping Point: A Case of New-Onset Primary Hyperparathyroidism in the Hospital

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Case Presentation

An 82-year-old male veteran with dementia (Alzheimer's vs. vascular) and depression was evaluated on the neuropsychiatry unit for a new incidental hypercalcemia.

In addition to depression and dementia, the patient has multiple medical problems including coronary artery disease, s/p CABG, ischemic cardiomyopathy with pacemaker, atrial fibrillation on chronic anticoagulation, and Bell's palsy treated with botulinum toxin injections.

On hospital day 26, his calcium was found to be 11 mg/dL and over the next three days rose to 13 mg/dL. He concurrently developed hypernatremia to 150 mmol/L. The patient was not overtly symptomatic; he did not display gastrointestinal or renal effects, bone pain, or muscle weakness that was markedly different than his baseline deconditioning. However, the hypercalcemia was possibly contributing to his psychiatric presentation, which included confusion, impulsivity, and irritability. The patient was started on aggressive fluid resuscitation and eventually cinacalcet per the recommendations of the Endocrinology service. Serum PTH returned high at 199 pg/mL. 25(OH) Vitamin D level was low at 20, while 1,25(OH) Vitamin D level was normal at 40. SPEP, UPEP, and PTHrP were unrevealing. Parathyroid imaging was deferred as the patient was not a surgical candidate due to his deconditioning, comorbidities, and ongoing altered mental status. With the above interventions, his sodium and calcium normalized. By the time of discharge from the hospital on HD 60, his alertness had improved, but his mental status was still quite far off baseline per his family. This case illustrates a rare and real-time presentation of hypercalcemia from hyperparathyroidism that was unmasked during his hospitalization.

Background

The incidence of Primary Hyperparathyroidism (PHPT) in the United States is 100,000 patients annually with a prevalence of 0.2-1%.[1] The incidence is on the rise as more patients receive relevant screening blood tests such as serum calcium and parathyroid hormone during workup for other conditions such as bone mineral screening.[2]

Primary hyperparathyroidism is characterized by PTH overproduction, usually by an adenoma. The vast majority are sporadic (90-95% of cases) with some familial cases (5%).[3] Moreover, 80-89% of cases involve an adenoma in one parathyroid gland and 4-5% involve two glands.[3,4] The adenoma is occasionally found in the thymus due to incomplete migration during embryogenesis.[5] About 6% of cases are characterized by glandular hyperplasia, usually of all 4 glands. Finally, parathyroid carcinomas account for about 1% of cases.[4]

Secondary hyperparathyroidism can be caused by vitamin D deficiency and chronic kidney disease. Additionally, it may be prudent to explore other causes of hypercalcemia, such as malignancy, familial hypocalciuric hypercalcemia, and medication effect.

Initial presentation

An incidental finding of mild hypercalcemia is the first presentation of primary hyperparathyroidism in 60-80% of cases. Modern patients typically do not exhibit the "bones (bone pain), kidney stones, abdominal groans, and psychic groans" that are classically-taught symptoms of the disease.[6] More patients are asymptomatic when diagnosed, but if carefully questioned may endorse mild symptoms of low energy and mood, forgetfulness, sleep disturbance, GERD, and constipation.[3,6-8] Catabolic effects on cortical bone (i.e., the distal third of the forearm) can be seen on DXA even in asymptomatic patients with sparing of trabecular bone.[9] These subclinical symptoms are more easily overlooked in the elderly population as they can be attributed to "normal aging" or multiple comorbidities. Calcium level does not always correlate with severity of disease.[6] Atypical presentations can vary from parathyroid crisis with severe hypercalcemia to normocalcemic PHPT. The next most common presentation is a chronic history of renal stones and intermittent or mild hypercalcemia (20-25% of cases). Finally, 5-10% of patients present with severe symptomatic hypercalcemia as well as osteitis fibrosa cystica,[7] which is characterized by osteoclast over-activation resulting in weakening of the bone structure.

Diagnosis

The initial differential for an elevated calcium is broad, and workup includes clinical evaluation, review of cancer screenings, and laboratory studies. It is important to exclude malignancy by ensuring that cancer screenings are up-to-date. An elevated or inappropriately normal serum PTH level is

suggestive of primary hyperparathyroidism, though elevated PTH can also be caused by medications, chronic kidney disease, malabsorption syndromes, and vitamin D deficiency.[2] Urine calcium is typically normal or high in PHPT, though it can be low if there is a concomitant vitamin D deficiency. To distinguish this disease from Familial Hypocalciuric Hypercalcemia (FHH), the urine calcium must be re-measured after repletion of vitamin D. In PHPT, the urine calcium should increase once the patient is vitamin D replete, whereas it will remain low in FHH. Vitamin D deficiency should be treated cautiously as vitamin D supplementation can lead to the unmasking of primary hyperparathyroidism. Lithium and Thiazide therapy can also unmask of PHPT.[7]

Once the diagnosis of PHPT is made, the clinician obtains DXA (at three sites, including the distal forearm) as well as vertebral and renal imaging in order to screen for an indication for surgery.[9,10] Imaging of the parathyroid gland is completed to assess for specific etiology, which guides treatment. Choices for imaging study are plentiful and varied, and it would be prudent to explore the available modalities and preferences at a particular institution. Commonly, Sestamibi (SPECT) scan and CT parathyroid protocol are available and appropriate.[3,4]

Treatment

Initial treatment of PHPT may focus on the control of hypercalcemia, if levels are >14 mg/dL or if the patient is symptomatic. Standard treatment includes hydration along with calcitonin, bisphosphonates, or even dialysis depending on the clinical situation.

Left untreated, PHPT progresses in about one-third of patients.[11] Indications for surgery include clinical symptoms, increase in calcium >1 mg/dL above the upper limit of normal, age <50, significant decrease in BMD compared to prior or osteoporosis, fragility fracture, renal stones, creatinine clearance <60cc/min, urine calcium >400 mg/24 h and nephrocalcinosis.[3,9,10] Treatment is surgical parathyroidectomy with high cure rates,[4] and medically managed if above criteria are not met or if contraindicated by medical comorbidity. The trend is toward more minimally-invasive surgery for adenoma removal, in attempt to reduce procedure risk, and cure is defined as normocalcemia six months after resection.[3]

Patients who are not surgical candidates require close medical management, which involves annual calcium and PTH, with DXA every 1-2 years until a surgical indication is met. These patients may also benefit from treatment of Vitamin D deficiency, low BMD, and hypercalcemia.[12] Cinacalcet is a calcimimetic that provides negative feedback to the parathyroid gland, resulting in lower PTH and, therefore, calcium levels in the blood. Cinacalcet is helpful in patients with symptomatic or severe hypercalcemia.[12] Bisphosphonates such as alendronate inhibit bone resorption and so can be useful in PHPT patients with osteoporosis.[10] However, it is important to keep in mind that bisphosphonate holidays may be indicated after the first several years of treatment in order to decrease the risk for atypical fracture.[13]

This case illustrates a unique presentation of primary hyperparathyroidism. It is unclear what triggered our patient's seemingly subacute presentation of this condition. He was not taking vitamin D, lithium, or any thiazide diuretics. It is possible that we witnessed a de novo development of the disease as he was relatively stable during this time on the neuropsychiatric ward. It is difficult to determine to what extent his hypercalcemia contributed to his psychiatric disturbance as his hospital course was long and complicated, and he had a component of delirium in addition to his underlying dementia and depression. Parathyroid imaging was deferred as he was deemed a poor surgical candidate, and he was scheduled for follow-up in the UCLA Endocrinology clinic. He was discharged to a skilled nursing facility and eventually transferred to the Veteran's State Home memory unit in West Los Angeles.

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