CLINICAL VIGNETTE

A Case of Primary Hyperparathyroidism in the setting of Normal Calcium Level

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Case

A 49-year-old woman presents with a chief complaint of "feeling very tired." For the past several months, she has not been able to perform her job as a nurse at the Intensive Care Unit without feeling fatigued. She has gained 30 pounds over the past year. Recent labs at another facility were reportedly normal. She was diagnosed with depression and was prescribed with duloxetine and armodafinil by her physicians. Her past medical history includes Hashimoto's thyroiditis, multinodular goiter, and obesity. Her past surgical history includes hysterectomy and bilateral salpingoophorectomy done for fibroids 5 years ago. Social history is unremarkable. On review of systems, she admits to having constipation "all the time" and denies depressive symptoms. In addition to duloxetine and armodafinil, she has been taking levothyroxine 88 mcg daily. On physical exam, her vital signs are normal with a BMI of 36. Her physical exam, including her neck exam, is normal. Her labs included normal kidney function, normal TSH, and Free T4. Calcium was high normal at 10.4 with albumin of 4.6. Liver enzymes were significant for elevated alkaline phosphatase at 139. After these initial laboratory studies, PTH was elevated at 109 with a normal ionized calcium of 1.3. CT of the neck with contrast showed bilateral multiple hypervascular parathyroid glands, which were greater than 10 mm. She underwent parathyroidectomy without complications. The biopsy showed hyperplasia. After the surgery, she continued to experience fatigue and had new symptoms of muscle spasm. Her calcium was low at 8.5, which improved with oral calcium carbonate, and by 6 weeks after the surgery, her fatigue fully resolved. She stopped Duloxetine and Nuvigil with no recurrence of fatigue.

Discussion

This case illustrates the importance of subtle deviations from reference range of serum calciums and the value of a thorough history to make the correct diagnosis for calcium metabolism disorders. Careful assessment of potentially reversible causes of depression and chronic fatigue may prevent mortality and morbidity. Though it may vary by laboratory, a serum calcium between 9 and 10.5mg/dL is considered normal. Mild hypercalcemia is defined as calcium above the upper limit of normal but below 11.5 mg/dL.[1] At this level, patients may report nonspecific symptoms such as fatigue, constipation, trouble concentrating, personality changes, or depression. Conversely, they may be asymptomatic. Patients with more severe hypercalcemia (greater than 12-13 mg/dL), particularly if it develops acutely, may present with nausea, anorexia, polyuria, pancreatitis, nephrolithiasis, lethargy, or coma. With long standing hyperparathyroidism, patients may experience bone pain or pathologic fractures. It can also cause bradycardia, AV block, or short QT interval. The most common cause of chronic hypercalcemia is primary hyperparathyroidism followed by underlying malignancy.

Before starting a diagnostic workup, it is important to rule out a false-positive laboratory test from hemoconcentration or elevation in serum albumin. First, the serum calcium should be corrected for the serum albumin level or by obtaining an ionized calcium. It is worth noting that both corrected calcium and ionized calcium in this patient were still in the normal range. Next, the PTH level should be obtained. If the PTH level is elevated (or "inappropriately normal") in the setting of elevated calcium and low phosphorus, the diagnosis is almost always primary hyperparathyroidism. If PTH is suppressed, it is most commonly due to underlying malignancy or less frequently from granulomatous disorders. In renal disease, both PTH and phosphorus are elevated.

Primary hyperparathyroidism has a peak incidence between the third and fifth decades (as in this patient). Parathyroid tumors are usually isolated adenomas but can occur as MEN syndromes. It is usually from a single gland neoplasm, but in 15% of patients, all glands are hyperfunctioning. It is rarely carcinoma, though suspicion for carcinoma is raised if calcium is above 14-15 mg/dL in the setting of parathyroid gland enlargements. Medical management with pharmacologic agents (such as cinacalcet and bisphosphonates therapy) is an option for patients who cannot or do not want to undergo surgery or who have persistent disease despite the surgery.[2]

In asymptomatic patients with primary hyperparathyroidism, close monitoring (i.e., annual labs and bone density testing) is justified unless they meet the criteria for surgery. These include serum calcium more than 1mg/dL above normal, age less than 50, T score less than -2.5 on bone density test, or creatinine clearance of less than 60 mL/min. Despite randomized studies showing no major benefits after surgery in this patient group, evidence favoring surgery is growing due to concerns about skeletal, cardiovascular, and neuropsychiatric diseases even in mild hyperparathyroidism. A 2013 study of twenty-two patients with elevated PTH but normal corrected serum calcium levels were observed for 12 months.[3] Three patients developed hypercalcemia, and one had parathyroidectomy. This study,

along with this clinical scenario, suggests the importance of the early recognition of hyperparathyroidism even in the setting of a "normal" calcium level.

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