CASE REPORT

A Challenging Case of Hypercalcemia

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The authors report a case of hypercalcemia in a 79-year-old woman that led to multiple hospitalizations. The case was challenging because the hypercalcemia was ultimately found to have 2 distinct causes. The patient initially presented with an elevated parathyroid hormone (PTH) level, consistent with primary hyperparathyroidism. She underwent parathyroidectomy and her hypercalcemia resolved in the immediate postoperative period. Four days after the operation, she was found to have recurrent hypercalcemia with a suppressed PTH level, raising suspicion for hypercalcemia of malignancy. After an extensive workup, the patient was found to have lymphoma, which was causing hypercalcemia and suppressing PTH. The authors also review the literature on hypercalcemia of malignancy.

Report of Case

A 79-year-old white woman was admitted to the hospital for evaluation of hypercalcemia. Her primary care physician referred her to the emergency room after outpatient laboratory testing showed a serum calcium level of 15.8 mg/dL (reference range, 8.3-10.2 mg/dL); the blood sample had been obtained a few days earlier. When questioned further, the patient stated that she had been experiencing nausea and worsening fatigue during the past several months, along with constipation, poor appetite, and a 4.55-kg weight loss that she had attributed to decreased appetite.

The patient had a medical history of hypertension and osteoporosis and had undergone an appendectomy as a child. Her mother had died of breast cancer in her 30s, and her father had had melanoma. She was a lifelong nonsmoker, and her outpatient medications included furosemide, potassium, carvedilol, amlodipine, aspirin, and raloxifene. She denied use of any supplements or vitamins.

Results of initial laboratory tests in the hospital indicated acute kidney injury, with a serum creatinine level of 2.44 mg/dL; the patient’s baseline creatinine level was 0.97 mg/dL in outpatient tests completed 8 months before admission. Her initial serum calcium level in the hospital was 15.8 mg/dL, and her serum parathyroid hormone (PTH) level was 96 pg/dL (reference range, 15-65 pg/dL). After intravenous hydration and treatment with intravenous pamidronate (60 mg), her calcium level decreased to 12 mg/dL and her creatinine level to 1.41 mg/dL. On the basis of these laboratory results, primary hyperparathyroidism was diagnosed. The patient declined surgical intervention, so medical treatment was initiated with cinacalcet hydrochloride (30 mg twice daily; an off-label use at the time). The patient was discharged to home and told to return to the endocrine office in 1 month for follow-up with repeated basic metabolic panel and PTH level testing.

Hypercalcemia has several known causes, with primary hyperparathyroidism and malignancy accounting for approximately 90% of cases.1 Other causes include tertiary hyperparathyroidism, familial hypocalciuric hypercalcemia, hyperthyroidism, drug effects, sarcoidosis, tuberculosis, and immobilization.1 We report the case of a 79-year-old woman with multiple hospitalizations for persistent hypercalcemia. She was ultimately found to have 2 distinct causes for her hypercalcemia. A thorough medical history and laboratory evaluation helped differentiate between these causes.
Approximately 1 month after hospital discharge, the patient had an office visit. She had been taking cinacalcet for 1 month but was experiencing pruritus, so the medication was discontinued. Results of laboratory tests after 1 month of cinacalcet treatment showed the following values: calcium, 12.3 mg/dL; PTH, 160 pg/dL; 25-hydroxyvitamin D, 42.1 ng/mL (reference range, 30-100 ng/mL); 1,25 dihydroxyvitamin D, 238 pg/mL (reference range, 19-67 pg/mL); and creatinine, 1.16 mg/dL. The patient still reported nausea and fatigue. Because of her inability to tolerate medical treatment and her persistently elevated calcium levels, surgery was proposed again as the preferred treatment option, and she agreed to surgical treatment. A sestamibi scan showed increased uptake bilaterally in the inferior part of her neck, suggestive of bilateral inferior parathyroid adenomas, and she was referred for surgery.

One week after being seen in our office and before her scheduled referral to the surgeon, the patient was readmitted to the hospital with symptomatic hypercalcemia. She had worsening fatigue and anorexia, and outpatient laboratory tests on blood samples obtained 1 day earlier showed calcium and albumin levels of 15.7 mg/dL and 3.0 g/dL, respectively (corrected calcium, 16.5 mg/dL). She was readmitted and, after treatment with parenteral hydration and intravenous pamidronate, similar to that given during her first hospitalization, her calcium level decreased to 12.7 mg/dL. Her PTH level was 105.8 pg/dL. The surgeon was consulted about performing parathyroidectomy for persistent symptomatic hypercalcemia secondary to primary hyperparathyroidism and ordered a second sestamibi scan. Unlike the initial outpatient scan, the second scan failed to demonstrate the location of the adenoma.

The patient underwent parathyroidectomy on hospital day 7. Her preoperative PTH level was 117.8 pg/dL. All 4 parathyroid glands were identified intraoperatively and removed. Half of the patient’s right superior parathyroid gland was reimplanted into her left forearm. Her postoperative PTH level was 11.6 pg/dL, and her postoperative calcium level was 9.4 mg/dL. Pathologic findings after parathyroidectomy were consistent with a left inferior parathyroid adenoma, which was hypercellular, weighed 200 mg, and measured 1.0 cm × 0.6 cm × 0.4 cm. The left superior, right inferior, and right superior parathyroid glands were all normal in cellularity and size. The patient was discharged to home on postoperative day 2, with plans for follow-up in the endocrinology office in 2 weeks. She did not require calcium or vitamin D supplementation at discharge.

Two days after discharge, the patient was readmitted for acute onset of shortness of breath. Computed tomographic angiography showed no evidence of pulmonary embolism. Initial laboratory test results revealed a calcium level of 10.8 mg/dL, which trended up to 11.7 mg/dL during the next several days. Her concurrent intact PTH level was undetectable (<1 pg/dL), and a cause for hypercalcemia other than hyperparathyroidism was therefore considered. Occult malignancy was suspected, and a workup for cancer was initiated. Serum and urine protein electrophoresis results were negative, the PTH-related protein (PTHrP) level was 8 pg/mL (reference range, 14-27 pg/mL), the 25-hydroxyvitamin D level was low (19 ng/mL; reference range, 30-100 ng/mL), and the 1,25 dihydroxyvitamin D level was elevated (131 pg/mL; reference range, 18-72 pg/mL). Results of a full-body bone scan were unremarkable, but computed tomography of the abdomen and pelvis demonstrated a large (12.6-cm) retroperitoneal soft-tissue mass surrounding the aorta. Fine-needle aspiration of the mass demonstrated a diffuse large B-cell lymphoma. The prognosis was deemed to be very poor and was discussed with the patient and her family, who decided that she should receive hospice care; she died of her disease 2 days later.
Comment

The most common cause of hypercalcemia in a hospitalized patient is cancer. Hypercalcemia of malignancy has several mechanisms, including direct osteolytic metastases and humoral hypercalcemia of malignancy, in which the tumor elicits either PTHrP or 1-α-hydroxylase.

Direct bone metastasis causes local osteolysis, resulting in hypercalcemia. Bone metastases stimulate the production of several osteoclast-activating factors, leading to bone resorption; these factors include interleukin 1 and 6 and tumor necrosis factor α. Tumors that commonly metastasize to bone include breast, prostate, renal cell, and non–small-cell lung carcinoma. Multiple myeloma also can cause hypercalcemia due to local osteolysis.

Calvani et al investigated the excessive bone resorption seen in multiple myeloma. They found that some of the B lymphocytes in patients with multiple myeloma can transform into osteoclast-like cells in vitro. They also found that the receptor activator of nuclear factor-κB ligand (RANK-L) promoted in vitro osteoclast formation from myeloma lymphocytes.

Mundy classified bone metastases as either osteolytic or osteoblastic. Osteoclast-activating factors released by tumor cells are responsible for osteolytic lesions, and tumor cell production of factors that stimulate osteoclast proliferation, such as fibroblast growth factors, bone morphogenetic proteins, platelet-derived growth factor, and transforming growth factor β, are responsible for osteoblastic metastases. Markers of increased osteoclastic activity, and therefore bone resorption, include urinary hydroxyproline, deoxypyridinoline, and pyridinoline cross-links. Markers of increased osteoblastic activity include alkaline phosphatase, osteocalcin, and increased uptake of bone-scanning agents. Most cancers that metastasize to bone have both osteolytic and osteoblastic properties. Breast cancer leads to predominantly osteolytic bone metastases, with some blastic lesions, whereas prostate cancer metastases are predominantly osteoblastic, with some lytic lesions; multiple myeloma, however, causes osteolytic bone lesions exclusively, without an osteoblastic component.

Because PTHrP is molecularly similar to intact PTH at the N-terminal sequence, it can bind to PTH receptors and mimic the action of PTH. Tumors that typically secrete PTHrP include those of squamous cell origin, including squamous cell carcinoma of the lung, head and neck, bladder, and esophagus; breast carcinoma, renal cell carcinoma, and lymphoma have also been shown to produce PTHrP.

Kitazawa et al presented a case of multiple myeloma with hypercalcemia secondary to production of PTHrP. They described the several mechanisms of hypercalcemia typically seen in multiple myeloma, including skeletal lesions and cytokine production from myeloma cells that further accelerate osteoclastic bone resorption.

Some malignancies can elicit 1-α-hydroxylase, the enzyme responsible for the conversion of 25-hydroxyvitamin D to its active form, 1,25 dihydroxyvitamin D, and activated vitamin D increases gastrointestinal absorption of calcium. Both Hodgkin and non-Hodgkin lymphoma have been shown to secrete 1-α-hydroxylase; this mechanism of hypercalcemia is similar to that seen in granulomatous diseases, such as sarcoidosis and tuberculosis, in which the granulomas can produce 1-α-hydroxylase.

Overbergh et al studied the intracellular pathways of the immune system involved in the regulation of 1,25 dihydroxyvitamin D production. They found that, after stimulation by inflammatory mediators such as interferon γ, macrophages produce 1-α-hydroxylase. They further noted that the production of 1-α-hydroxylase by macrophages is regulated mainly by immune signals, whereas the production of this enzyme at the level of the kidney is regulated by PTH. Seymour and Gagel also noted that macrophages can express 1-α-hydroxylase and are responsible for the hypercalcemia seen in granulomatous diseases; it is believed that activated macrophages also play a role in lymphoma-associated hypercalcemia.

Several treatment strategies are available for hypercalcemia as a result of malignancy. For all forms of hypercalcemia, important measures include discontinuation of calcium and vitamin D supplements and any other drugs that can worsen the hypercalcemia, such as...
lithium and thiazide diuretics, as cautioned by Stewart\(^1\) in his review of hypercalcemia of malignancy. Stewart\(^1\) recommended repletion of phosphorus levels in patients with serum levels of 2.5 mg/dL or less because phosphorus acts as an intraluminal calcium binder. Volume expansion with parenteral fluids followed by administration of a loop diuretic can be helpful in achieving calciuresis and lower serum calcium levels; loop diuretics should be withheld in dehydrated patients until the intravascular volume is replete with fluids.\(^3\) Intravenous bisphosphonate therapy can also be used to lower serum calcium levels in hypercalcemia of malignancy by blocking osteoclastic bone resorption.\(^11\)

The use of calcitonin to treat patients with hypercalcemia is limited owing to its inability to dramatically lower serum calcium levels.\(^11\) Mithramycin is a treatment option, but potential serious adverse effects limit its use, including thrombocytopenia, platelet aggregation defect, anemia, leukopenia, hepatitis, and renal failure.\(^11\) Gallium nitrate is also an option but needs to be given as a continuous infusion for 5 days.\(^11\) Dialysis can be considered in patients with hypercalcemia who have severe, acute kidney injury or chronic renal insufficiency.\(^11\)

For patients with 1-α-hydroxylase–mediated hypercalcemia, glucocorticoid therapy should be considered. Glucocorticoids reduce serum calcium levels by inhibiting the enzyme 1-α-hydroxylase. Glucocorticoid therapy may be beneficial in other forms of hypercalcemia of malignancy by decreasing tumor production of cytokines, thus inhibiting osteoclastic bone resorption.\(^11\)

Denosumab, a RANKL-targeted monoclonal antibody used to manage osteoporosis, is currently being studied in clinical trials. Boiko and Hammers\(^13\) described a patient treated with denosumab for hypercalcemia as a result of metastatic renal cell carcinoma. The patient’s hypercalcemia was refractory to treatment with zoledronic acid, but after treatment with denosumab his calcium level normalized and remained in a normal range for several weeks.

**Conclusion**

The differential diagnosis for hypercalcemia is extensive, and the treatments vary drastically depending on the underlying condition. The case we report was difficult to diagnose because the patient had 2 distinct diagnoses leading to hypercalcemia. It is important to be vigilant in evaluating a patient with a persistent abnormality and remember that the initial diagnosis can be confounded by an additional diagnosis.

**References**