

CLINICAL VIGNETTE

Acute Renal Failure, Hypercalcemia, and Elevated Calcitriol Levels

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Clinical Case

A 56-year-old man was re-admitted to the hospital with recurrent acute renal failure and hypercalcemia. On his index admission, patient presented with abdominal pain in association with nausea and vomiting. Medical history was notable for diabetes mellitus type 2 and hypertension. As an outpatient he was receiving therapy with oral hypoglycemic medications as well as hydrochlorothiazide for blood pressure control. At that time, biochemical evaluation showed acute kidney injury and hypercalcemia which were attributed to pre-renal azotemia from dehydration and concurrent use of a thiazide diuretic.

During the current admission the patient was noted to have normocytic anemia and a Hematology consultation was requested. The patient had no numbness or tingling of extremities. No history of recurrent infections requiring antimicrobials. He denied fevers, cough, or night sweats. He did report weight loss of twenty-five pounds over the last two months. Pertinent laboratory evaluation included hemoglobin 12.1 gm/dL (normal 13 – 18 gm/dL), serum creatinine 2 mg/dL (normal 0.6 – 1.3 mg/dL), calcium 14.5 mg/dL (normal 8.5 to 10 mg/dL), and ionized calcium 1.99 mmol/L (normal 1.11 – 1.3 mmol/L). Serum protein electrophoresis showed a normal pattern without a monoclonal protein. He had elevations of both immunoglobulins A and G and mild increased levels of both kappa and lambda free light chains. Additional labs include low intact PTH hormone level of 10 pg/mL (normal 15 – 65 pg/mL), PTH-related peptide < 2 pmol/L (normal 0.0 – 2.3 pmol/L), 25-OH vitamin D level low at 22.7 ng/mL (normal 30 – 100 ng/mL), 1,25-OH vitamin D level elevated at 90.1 pg/mL (normal 19.9 – 79.3 pg/mL) and angiotensin converting enzyme (ACE) level < 5 units/L (normal 9 – 67 units/L). He had normal PSA level, negative Quantiferon-TB gold as well as negative viral hepatitis and HIV serologies. Non-contrast CT of neck, chest, abdomen, and pelvis revealed bilateral peri-lymphatic lung nodules and evidence of hepatosplenomegaly with no bony lytic lesions. A bone scan was normal as well as transthoracic echocardiogram. Bone marrow core biopsy and aspiration showed a normocellular marrow with no evidence of hematologic malignancy. Congo Red stain was negative and cytogenetics showed a normal male chromosome pattern. CT-guided biopsy of right kidney showed pathological findings compatible with acute tubular injury, diabetic glomerulosclerosis, arterial and arteriolar nephrosclerosis as well as evidence of chronic and active interstitial nephritis. He was discharged from hospital and developed recurrent hypercalcemia which responded promptly to repeat dose of intravenous

zoledronate. PET/CT scan showed similar pulmonary findings to previous CT as well as diffuse and increased metabolic activity of spleen. He was evaluated by Pulmonary for persistent peri-lymphatic lung nodules. Bronchoscopy with trans-bronchial biopsy revealed granulomatous changes consistent with sarcoidosis. He was started on immunosuppressive therapy with prednisone and mycophenolate mofetil with dramatic improvement of kidney function and serum calcium levels.

Discussion

Hypercalcemia can be seen in patients with and without an underlying malignant neoplastic process. The clinical presentation in most cases is similar with symptoms including general malaise, impaired concentration, nausea, vomiting, abdominal pain, and constipation. Etiologies of non-malignant hypercalcemia may include primary hyperparathyroidism, granulomatous diseases, thyrotoxicosis, medications, as well as rare genetic disorders. Either hematologic or oncologic malignancies can be observed in patients experiencing cancer-related hypercalcemia. Some of the common solid organ malignancies associated with development of hypercalcemia include breast cancer, lung cancer, and renal cell carcinoma as well as head and neck squamous cell cancer. Hypercalcemia is also seen in patients with underlying hematologic malignancies such as Hodgkin's lymphoma, aggressive high-grade Non-Hodgkin's lymphoma, and plasma cell disorders such as multiple myeloma. In general, hypercalcemia is considered mild if total serum calcium level is between 10.5 and 12 mg/dL. In contrast, total serum calcium levels above 14 mg/dL can be life threatening.¹

The pathophysiology of cancer-related hypercalcemia can involve overlapping mechanisms in both solid and hematologic malignancies. Three common mechanisms have been described: (1) humoral hypercalcemia of malignancy; (2) hypercalcemia associated with skeletal metastases, (3) and hypercalcemia associated with hematologic malignancies.² Humoral hypercalcemia of malignancy (HHM) is characterized by elevated calcium levels in blood in the absence of skeletal metastasis. Studies have shown HHM to be mediated by elevated levels of parathyroid hormone-related peptide (PTHrP). This results in increased bone resorption and decreased calcium clearance by the kidneys.³ Similarly, patients with radiographic evidence of skeletal metastases develop

hypercalcemia mainly from local osteolysis mediated by tumor cells. On the other hand, patients with hematologic malignancies can develop elevated calcium levels with or without osteolytic bone destruction. In patients without bone lytic lesions, hypercalcemia is not uncommonly noted in association with elevated levels of 1,25-dihydroxyvitamin D₃ (calcitriol).³ As has been well described, vitamin D₃ (cholecalciferol) ingested from diet is hydroxylated in the liver to its major circulating form 25-hydroxyvitamin D₃ (calcidiol). In the proximal renal tubule, this metabolite is again hydroxylated to biologically active calcitriol.⁴ In patients with granulomatous diseases and hematologic malignancies, increased enzymatic activity of extra-renal 25-hydroxyvitamin D-1 α -hydroxylase in tissue macrophages results in increased levels of calcitriol.⁵ This leads to increased intestinal calcium absorption and bone resorption, and hence hypercalcemia.

Patients who present with severe and symptomatic hypercalcemia require immediate medical treatment. Most patients with symptomatic hypercalcemia are volume depleted because of polyuria induced by hypercalcemia. Administration of intravenous fluids with normal saline allows for rapid correction of volume deficit and reduces proximal tubular reabsorption of calcium. Volume repletion also permits subsequent use of loop diuretics to further enhance calcium excretion.⁶ Once initial resuscitative therapies have been implemented, lowering of serum calcium levels can be accomplished with the use of anti-resorptive medications. In the United States, the bisphosphonates pamidronate and zoledronate are approved for the treatment of malignancy-associated hypercalcemia. These agents block osteoclast-mediated bone resorption by inducing osteoclast apoptosis.⁶ Typically a clinical response is seen within two to four days with a nadir in serum calcium within four to seven days. Caution is required because acute kidney injury has been reported with rapid intravenous administration of bisphosphonates. Denosumab is an alternative to bisphosphonates in the treatment of hypercalcemia of malignancy. Denosumab is a fully human monoclonal antibody that binds RANKL (receptor activator of NF κ B ligand) in extracellular fluid and prevents RANKL binding to RANK receptor on the osteoclast surface.⁷ The end result is inhibition of osteoclast activity and inhibition of bone resorption. Denosumab is approved for treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy. In this setting responses are reported in sixty-four percent of patients.⁸ Alternative therapeutic options for correction of cancer-related hypercalcemia include calcitonin and glucocorticoids with limited therapeutic efficacy, due in part to short duration of action and tachyphylaxis.

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