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CLINICAL VIGNETTE

Hypercalcemia Associated with Diffuse Large B Cell Lymphoma

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A 91-year-old-male with a single kidney due to remote prior left nephrectomy for renal mass presents with 3-4 weeks of generalized fatigue with worsened CKD. Past medical history was remarkable for nephrolithiasis, enlarged prostate, and chronic kidney disease (CKD) with baseline serum creatinine of 2 mg/dL (normal range 0.6-1.3 mg/dL) and estimated glomerular filtration rate (eGFR) of 34. Recent laboratory tests obtained by his primary physician revealed hypercalcemia with serum calcium of 12.6 mg/dL (reference range 8.7-10.5 mg/dL), serum albumin of 2.4 g/dL (reference range 3.9-5.0 g/dL), ionized serum calcium of 1.61mmol/L (reference range 1.09-1.29 mmol/L), and acute kidney injury (AKI), serum creatinine of 6.1 mg/dL on CKD. The patient was admitted for further evaluation. The patient's AKI was related to volume depletion and prerenal azotemia as well as hypercalcemia. He was treated with intravenous fluid, normal saline, and intravenous pamidronate with improvement in his AKI and hypercalcemia.

Evaluation for his AKI and hypercalcemia revealed serum parathyroid hormone (PTH) of 9 pg/mL (normal range 15-65), PTH-Related Peptide (PTHrP) of 31 (with reference range of 14-27 pg/mL), serum calcitriol [1,25(OH)₂ vitamin D₃] of 140 pg/mL (with reference range of 19.9-79.3 pg/mL), and serum 25-hydroxyvitamin D of 25 (with optimal level of 30-80 pg/mL). Urinalysis was unremarkable. Patient's urine and serum immunofixation were both negative for monoclonal antibody. CT-scan of abdomen/pelvis showed bulky retroperitoneal lymphadenopathy at the level of the renal veins highly concerning for metastatic disease. CT-scan of chest showed moderate multistation intrathoracic adenopathy in conjunction with permeative destruction of the sternum with associated soft tissue swelling/mass. Ultrasound guided biopsy of sternal mass showed diffuse large B cell lymphoma, germinal center type. The patient was not receiving any vitamin D or calcium supplements.

In the setting of low serum PTH level, slightly elevated PTHrP, and highly elevated serum calcitriol level in the patient, it is concluded that the patient's severe hypercalcemia is secondary to his increased serum calcitriol.

Discussion

There are several medical conditions associated with hypercalcemia. The pathophysiology of all of these conditions are involved with one or more mechanisms. These include

hypercalcemia associated with excess parathyroid hormone secretion as in primary hyperparathyroidism. This is usually associated with mild-to-moderate hypercalcemia. Increased intake of vitamin D or/and calcium supplements. Hypercalcemia secondary to medications such as thiazide diuretics and calcium-containing antacids resulting in milk alkali syndrome. Hypercalcemia associated with malignancy secondary to systemic production of PTHrP as in squamous-cell cancer, renal cancer, and bladder cancer. Release of cytokines from tumor cells that mediate local osteoclast activation and bone resorption with subsequent hypercalcemia such as multiple myeloma. Last hypercalcemia associated with ectopic 1-alpha hydroxylation of 25-hydroxyvitamin D resulting in increased levels of calcitriol [1,25(OH)₂ vitaminD₃] such as lymphoma and granulomatous disease (e.g., sarcoidosis, tuberculosis, and histoplasmosis).

More than 50% of patients who are admitted to the hospital with hypercalcemia have malignancy as the etiology.¹ In patients with malignancy-related hypercalcemia, hypercalcemia secondary to production of PTHrP is the most common cause (80%), followed by osteolysis secondary to release of cytokines (20%). Increased production of calcitriol as the cause of hypercalcemia is very rare condition in malignancy and accounts for less than 1% of cases and is most commonly seen in lymphomas.² In patients with lymphoma, almost 15% will develop hypercalcemia at some point during the course of their disease and is usually seen in patients with more aggressive tumors and usually mediated by elevated calcitriol.³ The ectopic 1-alpha hydroxylation of 25-hydroxyvitamin D by the lymphoma cells or/and tumor-infiltrating macrophages result in increase in the level of serum calcitriol.^{4,5} The extra renal production of calcitriol by these cells result in substantial increase in the absorption of calcium from intestine, raising serum calcium level. Normally, 1-alpha hydroxylase converts 25-hydroxyvitamin D to calcitriol under the control of PTH in response to hypocalcemia. In contrast, the 1-alpha-hydroxylase in lymphoma cells or tumor-infiltrating macrophages is poorly sensitive to feedback from circulating PTH, resulting in inappropriate calcitriol production and subsequent severe hypercalcemia.⁶

Patients with hypercalcemia are generally severely volume depleted and dehydrated. AKI secondary to pre-renal azotemia is common in this group of patients. Volume resuscitation is the cornerstone of treatment, followed by therapy to inhibit bone resorption, induce calciuresis, and treat the underlying cause of hypercalcemia.⁷ Glucocorticoids reduce the calcitriol production by macrophages are the therapy of choice in patients with calcitriol-mediated hypercalcemia.⁸

In conclusion, increased level of calcitriol is not a common cause of hypercalcemia. Clinicians should measure the serum calcitriol levels while they search for the underlying cause of hypercalcemia. Elevated levels of calcitriol with low levels of PTH and PTHrP suggest lymphoma or granulomatous diseases as the cause of hypercalcemia.

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