CLINICAL VIGNETTE

Treatment of Refractory Hypercalcemia of Malignancy in a Woman with Advanced Cervical Cancer

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Case

A 44-year-old female with depression and anxiety was re-admitted to the hospital for critically elevated calcium levels. She presented with weakness and falls and found to have hypercalcemia of unclear etiology [Figure 1]. Her initial evaluation included normal PTH, low parathyroid hormone-related protein (PTHrP) <2.0, normal thyroid stimulating hormone (TSH), low 25-hydroxy vitamin D and low 1,25-Dihydroxy-vitamin D (calcitriol). No monoclonal proteins were detected on serum and urine protein electrophoresis, and morning cortisol was normal. She received fluids and a dose of zoledronic acid. Her calcium normalized and she was discharged for continued outpatient evaluation. Since returning home, the patient has remained essentially bed bound, requiring increasing assistance. She reports reduced appetite and increased constipation, as well as suprapubic cramping pain. She also notes abnormally heavy menstrual bleeding and weight loss for the past year.

Upon re-presentation to the emergency room, initial vital signs included sinus tachycardia to 160 with normal blood pressure. She appeared weak and chronically ill and reported ongoing lower abdominal pain and abnormal vaginal bleeding. Initial labs included white count of 15.8/mm^3, hemoglobin 10.1g/dL, platelets 1214/mm^3, corrected Ca 15.8mg/dL. Urinalysis showed positive pyruria and she was started on broad spectrum antibiotics and intravenous fluids. CT abdomen and pelvis with contrast showed a large complex mass measuring 10.0 x 9.7 x 10.3 cm located at the cervix/lower uterine segment which was concerning for malignancy [Figure 2]. CT angiogram of chest was negative for pulmonary emboli or other lung pathologies.

Gynecologic oncology was consulted and tissue biopsy confirmed high grade cervical clear cell carcinoma. Due to the extensiveness of the mass and poor ECOG performance status, surgery was not considered. Repeat evaluation of hypercalcemia did not reveal a specific etiology. Recurrent hypercalcemia was treated with fluids and another dose of zoledronic acid, with normalization of calcium by discharge and follow ups with endocrinology, gynecologic oncology and medical oncology.

She was re-hospitalized with hypercalcemic discharge a few weeks after. Subsequent evaluation noted elevated PTHrP and 1,25-Dihydroxyvitamin D (calcitriol), which were low on initial testing. She received additional anti-resorptive therapy with denosumab and started on prednisone with hypercalcemia improvement. PET scan showed metastasis to pelvic lymph nodes without distant disease. There was no sign of granulomatous disease. She currently continues cisplatin chemotherapy and palliative radiation therapy.

Discussion

Hypercalcemia of malignancy (HCM) is a common complication of advanced stage cancers, with considerable morbidity. HCM may be mediated through the following non-PTH dependent mechanisms: (1) humoral PTHrP, (2) bone metastasis and (3) calcitriol mediated.[1] Around 30% of patients with malignancy develop hypercalcemia at some time. Common malignancies associated with hypercalcemia include lung, breast, colorectal cancers, renal cell carcinoma and multiple myeloma. Hypercalcemia is rare with gynecologic malignancies.[2]

Humoral hypercalcemia accounts for 80% of cases due to excess excretion of PTHrP. About 20% are due to osteolytic resorption related to bone metastases. Less than 1% is due to excess production of calcitriol.[2] A common misconception is that patients with PTHrP dependent HCM are unlikely to also have elevated calcitriol. One retrospective series of patients with PTH-independent HCM due to solid tumors reported 76% with elevated PTHrP.[3] Our patient's labs show both combined elevated PTHrP and excess calcitriol. Elevated calcitriol levels in patients with lymphomas and granulomatous disease are due to increased 1-alpha-hydroxylase activity of surrounding macrophages. These convert Vit D to active calcitriol. However, the dysregulation of calcitriol in solid tumors is less clear. In both hematologic malignancies and a few solid tumors, immunological histology stains show extrarenal expression and activation of 1-alpha-hydroxylase in nonmalignant as well as malignant cells.[2] These include normal colonic cells and tumor-associated macrophages. There is also no clear correlation of calcitriol with PTHrP elevation or with hypophosphatemia.[3]

Multiple mechanisms of HCM appear to contribute to refractory HCM. "Refractory" includes patients with reasonable control of calcium while hospitalized, receiving standard therapy (ie. intravenous fluids, calcitonin, antiresorptive agents) with

recurrence of severe hypercalcemia days to weeks after hospital discharge.[3] Calcitriol acts on calcium homeostasis by increasing bone resorption but also significantly increases intestinal absorption of calcium. This helps explain why patients with concomitant PTHrP and calcitriol mediated HCM may have an unsatisfactory response to standard antiresorptive therapy alone. Steroids are considered standard treatment for lymphomas and granulomatous causes of elevated calcitriol, but have also been used to treat refractory HCM in patients with solid tumors. The mechanism of action is by inhibiting extrarenal 1-alpha-hydroxylase leading to decreased intestinal absorption of calcium.[3] Additional recommendations include avoidance of calcium and vitamin D rich foods and supplements.

In conclusion, refractory HCM may lead to readmissions for severe hypercalcemia with standard antiresorptive therapy. It is important to target other involved pathophysiological mechanisms with the addition of steroids [Table 1]. The definitive treatment of HCM is the management of the tumor with antineoplastic therapy and/or surgery.

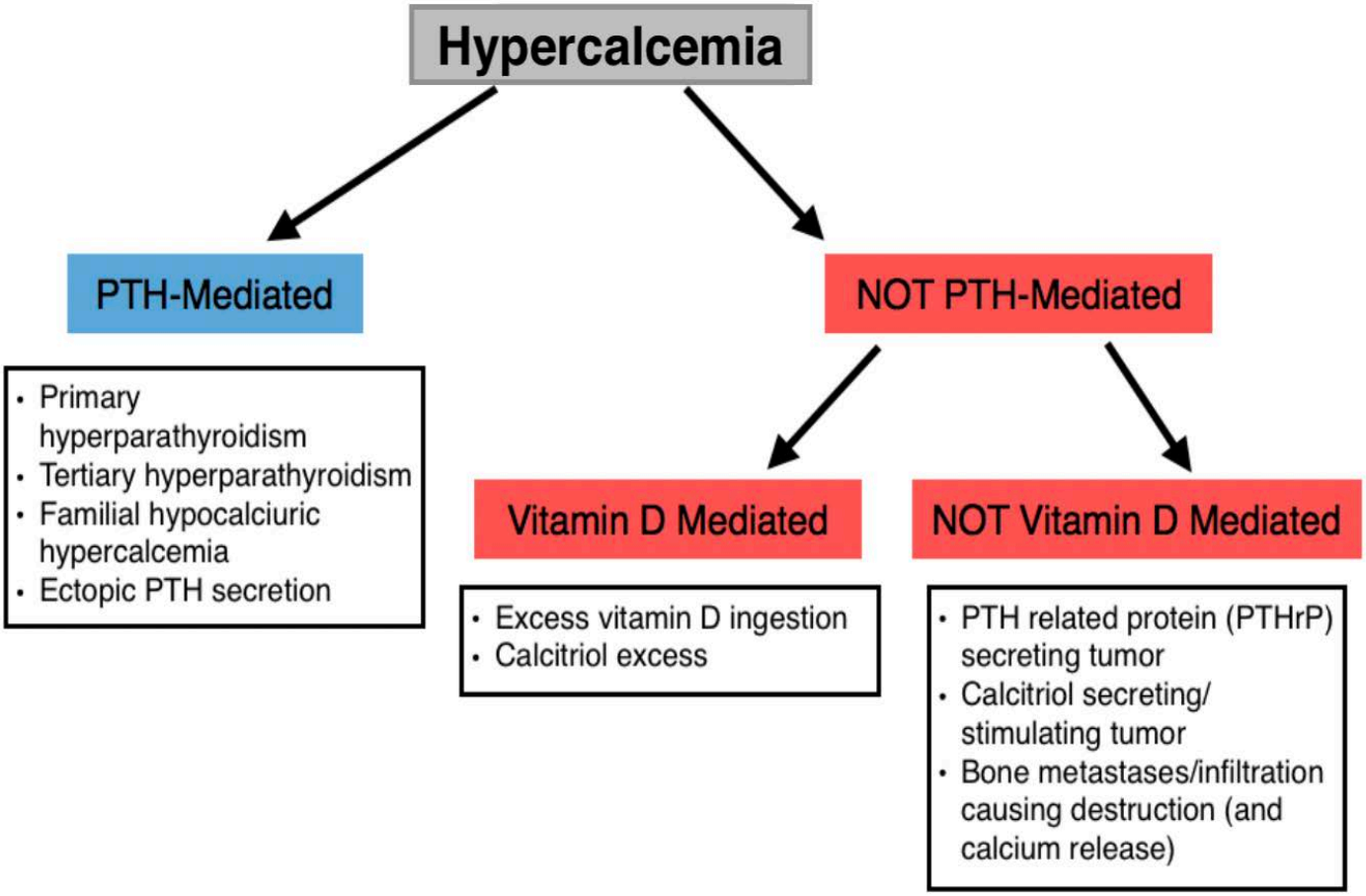

Figure 1. Causes of hypercalcemia

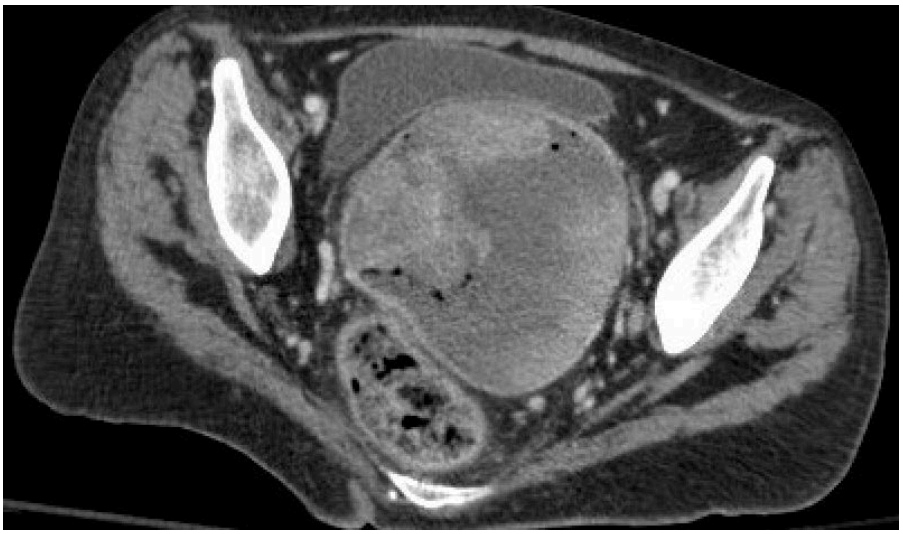

Figure 2.

Mechanism	Driver			Therapy targeted to contributory mechanism
	Endocrine		Other	
	Inappropriate calcitriol production	PTHrP production	Local osteolysis (advanced cancer in the bone)	
Bone resorption	+	+++	+++	Intravenous bisphosphonates, denosumab
Gastrointestinal calcium absorption	+++	*	–	Corticosteroids or other inhibitor of 1-alpha-hydroxylase; limit dietary calcium intake
Renal calcium reabsorption	–	+++	–	Frequent intravenous fluids (normal saline with furosemide); cinacalcet
Hypophosphatemia (less CaPO4 = increased serum calcium)	–	++	–	Oral phosphorus

Table 1: Endocrine mechanisms that contribute to PTH-independent refractory HCM, which specific therapies for each mechanism.[3]

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