

Refractory hypercalcemia of malignancy related to vitamin D toxicity: Treatment strategies

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ABSTRACT

Introduction: Hypercalcemia of malignancy (HCM) is a known cancer complication resulting in morbidity and mortality. It is most often mediated by parathyroid hormone related peptide (PTHrP) or direct bone invasion, but may be related to other humoral causes. Most cases of HCM respond to standard therapies such as fluids, loop diuretics, bisphosphonates, calcitonin, denosumab and control of the underlying malignancy. **Case Report:** This report describes the case of a 60-year-old woman with metastatic breast cancer and vitamin D toxicity who developed PTHrP driven HCM. The case is a unique example of breast cancer related HCM in the absence of bone metastases. The hypercalcemia was refractory to standard treatments including intravenous bisphosphonates, fluids and calcitonin. Ultimately, the patient responded to denosumab dosed every seven days along with daily intravenous hydration. Response was maintained despite failure to control the underlying malignancy. **Conclusion:** Vitamin D toxicity may exacerbate PTHrP driven HCM. Frequent dosing of denosumab is shown to

be safe and effective in refractory HCM. The mechanisms and management of vitamin D toxicity are reviewed.

Keywords: Hypercalcemia of malignancy, Osteoprotegerin (OPG), Parathyroid hormone related peptide (PTHrP), Receptor activator of nuclear factor kappa beta ligand (RANKL), Vitamin D

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INTRODUCTION

Hypercalcemia of malignancy (HCM) is a metabolic disorder defined by serum calcium greater than the upper limit of normal in the setting of cancer. It is estimated to affect about 2.0% of all cancer patients [1, 2] with the frequency varying by cancer type. Multiple myeloma has the highest incidence rate at 7.9%, although lung and breast cancer related HCM account for the most inpatient admissions. The symptoms of HCM are systemic, and include altered mental status, fatigue, bone pain, abdominal pain, kidney stones, nausea and vomiting. The mechanisms of HCM may be categorized into humoral-related causes, direct bone causes, and rare causes. The humoral causes may be subdivided into parathyroid hormone-related protein (PTHrP) related or non-PTHrP-related. For non-PTHrP-related humoral HCM, it is believed that cytokine signaling, parathyroid hormone

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signaling and vitamin D secretion may all play roles in promoting osteolysis [3, 4]. The cellular signals involved in bone microenvironment are the receptor activator of nuclear factor kappa beta (RANK) on the osteoclast, the RANK ligand on the osteoblast and osteoprotegerin (OPG), a decoy receptor which binds to and inactivates RANKL.

The HCM case described in the following report is unique in presentation and is instructional for management of refractory HCM. To the best of our knowledge, this is the first case report describing a case of severe humoral hypercalcemia in breast cancer without bone metastases. It is also a rare report of iatrogenic vitamin D toxicity. We further report on the ability to successfully manage refractory HCM in the absence of control of the underlying malignancy.

CASE REPORT

A 60-year-old female noted a right breast mass 18 months prior to presentation to the medical system. She initially sought care via alternative medicine and ingested mega doses vitamin D along with various other supplements. Prior to initial presentation, she took 10,000 units of ergocalciferol daily for several months. She presented to the emergency room with one week of generalized weakness, nausea and gastrointestinal complaints.

A laboratory workup revealed a total calcium of 14.0 mg/dL (normal range 8.5–10.5 mg/dL) with a 1, 25-(OH)₂ vitamin D₃ level of 100 pg/mL (normal range 18–78 pg/mL), a 25(OH) vitamin D₃ level of >150 ng/mL, parathyroid hormone (PTH) of 5.0 pg/mL (normal range 9–77), and PTHrP of 8.9 pmol/L (normal range < 2pmol/L). The initial presenting EKG did not reveal significant QRS nor T wave findings. Additional labs are listed in Table 1.

The examination revealed right axillary lymphadenopathy and an ulcerated scan breast tumor. The patient underwent a fine needle aspirate of the breast lesion that revealed an estrogen receptor positive adenocarcinoma. She also had a liver ultrasound which revealed multiple liver masses. A PET/CT scan (Figure 1) failed to reveal other organ or bone lesions, although lymphadenopathy was observed. She was managed with intravenous fluids, calcitonin intramuscularly thrice, furosemide daily and IV pamidronate during her first three days of inpatient treatment. She left the hospital at that point with calcium of 10.4 mg/dL, but declining anti-cancer treatment. The patient complied with the recommendation to drink at least 2 L of fluids daily.

The patient was re-admitted 13 days later with nausea and imbalance and a calcium level of 18.4 mg/dL. Intravenous saline and furosemide were administered along with the RANKL inhibitor, denosumab (120 mg subcutaneously). Over the course of three weeks, two additional doses of denosumab 120 mg and an additional

dose of pamidronate were administered due to persistently elevated calcium levels (ranging from 12–18 mg/dL). She received 2–4 liters of intravenous saline daily as an outpatient over the course of four weeks with regular furosemide and in addition to oral intake of greater than 2 L daily. Diet was strictly low calcium and vitamin D had been appropriately discontinued. The patient declined the use of steroids to prevent 1 α -hydroxylase activity mediated conversion of her vitamin D from 25-hydroxy to 1,25-dihydroxy vitamin D.

The patient had one of the most treatment-refractory HCM cases reported, yet this patient expressed strong opposition to inpatient hospital management of her disease. The opposition was due to the perception that life expectancy was very short. In terms of cancer management, it is notable that the patient's core biopsy of the right breast lesion revealed grade 3, invasive ductal carcinoma with apocrine features. The tumor had positive estrogen receptor expression, negative progesterone receptor expression, and a non-amplified human epidermal growth factor receptor erB-2 (Her2/neu). The patient was eventually treated with the aromatase

Table 1: Selected patient laboratories at presentation

Laboratory Name	Normal range	Measured Value
Alanine Aminotransferase	<55 U/L	130 U/L
Aspartate Aminotransferase	< 35 U/L	125 U/L
Total Bilirubin	0.3 – 1.2 mg/dL	0.6 mg/dL
Albumin	3.2 – 5.2 g/dL	4.2 g/dL
Cancer Antigen 15-3	< 31 U/ml	120 U/ml

Abbreviations: U/L units per liter

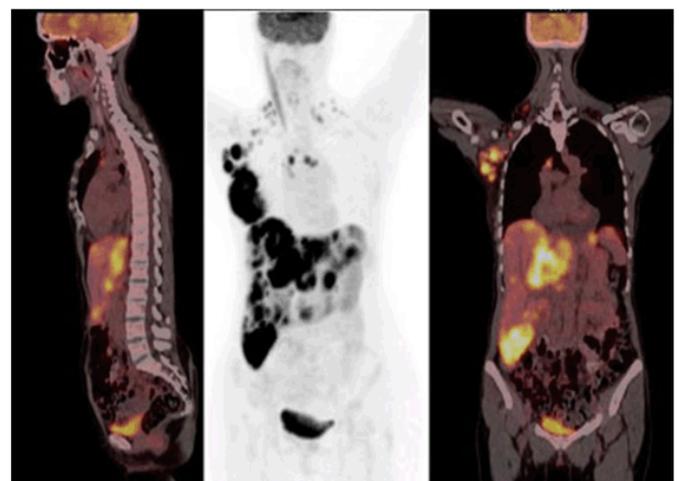


Figure 1: Fused PET/CT scan of patient at time of initial presentation. FDG uptake is demonstrated in the breast, axilla, liver, internal mammary and supraclavicular lymph nodes. The middle image is a maximal intensity projection of FDG uptake by in the coronal plane. There is a notable lack of bone metastases in these images.

inhibitor, letrozole. Chemotherapy and palbociclib were declined due to patient concerns regarding potential side effects. The patient experienced disease progression on single agent letrozole and sought alternative treatment rather than salvage therapy. Several months later, the patient declined all treatments and ultimately succumbed to fulminant liver failure.

DISCUSSION

Hypercalcemia of malignancy (HCM) is a well-recognized phenomenon and is associated most commonly with either elevated levels of PTHrP or bone metastases [5]. The classic presentation includes an elevated serum calcium in addition to renal stones, polyuria, dehydration, nausea, constipation, anorexia, lethargy, weakness, and confusion. In severe cases syncope from arrhythmias may occur as well as coma, renal failure or pancreatitis. The normal initial workup would include serum calcium, phosphorus, creatinine, PTH, and TSH along with imaging by chest radiography and/or imaging for bone metastases. A second step in the work-up would be the measurement of the PTHrP level. Typically, intravenous bisphosphonates, fluids, loop diuretics, and calcitonin are utilized for rapid reversal of HCM. In severe cases hemodialysis may be considered. In the case presented here with HCM mediated by PTHrP and vitamin D toxicity, the standard interventions were not sufficient. Recent studies have suggested that denosumab is an effective agent in cases of refractory hypercalcemia [6]. Denosumab is a fully human monoclonal antibody that binds to RANKL. Denosumab has been demonstrated in the past to prevent or reduce skeletal-related events or HCM in various advanced malignancies involving bone [7–9]. When routine bisphosphonates, fluids and calcitonin fail to mitigate the HCM, a protocol for weekly dosing of denosumab is appropriate for use [10] and was the only intervention to achieve HCM control in the case presented above. Thus in the case described, despite failing to achieve control of the underlying malignancy, the hypercalcemia was safely controlled to a safe range over the course of 5 weeks of treatment and nearly daily IV fluid support. The case presented highlights the occasional failure of IV bisphosphonates to control HCM, especially when driven by PTHrP or vitamin D toxicity. This case also highlights the utility of weekly denosumab for refractory HCM and the potential risk of over-supplementation with vitamin D in breast cancer.

In addition to utilization of inpatient and outpatient resources for daily IV fluid support, the morbidity of HCM is important to recognize. In this case, GI symptoms and CNS/psychiatric symptoms limited the quality of life in a breast cancer patient with a terminal disease. Some of the morbidity of the paraneoplastic HCM might have been averted by earlier presentation in this case, but it should be noted that HCM can present either early or

late in the course of malignancy. It is also noteworthy that HCM can occasionally be managed in the absence of underlying disease control as was the situation in this case. The more aggressive weekly use of a RANK-L inhibitor proved beneficial in this case. No adverse effects of weekly denosumab were observed. Specifically no dental, orthopedic or hypocalcemia events were encountered. The experience reported here confirms that super-therapeutic dosing of bone targeted therapies may be considered when HCM is refractory and the underlying cancer cannot be controlled. It may also be suggested that weekly denosumab may be useful for refractory HCM cases related to vitamin D toxicity.

This report highlights the role RANKL plays in PTHrP mediated HCM. PTHrP is responsible for HCM in 70% of breast cancer patients with advanced disease [5]. PTHrP exerts its effect primarily by binding to the parathyroid hormone (PTH) receptor. This results in two primary modes of action. First, osteoclastic bone resorption may occur via increased osteoblast RANK-L expression that leads to RANK activation on osteoclast precursors. Osteoclasts degrade the bone matrix via production of strong acids and proteinases [11]. Second, degradation of the bone releases tumor growth factor beta (TGF β) and other growth factors. These growth factors further stimulate tumor growth, increased levels of PTHrP, and ultimately a cycle of bone resorption which is difficult to interrupt. PTHrP further increases calcium reabsorption in the loop of Henle and inhibits phosphate reabsorption in the proximal convoluted tubule. Unlike PTH, the PTHrP does not increase 1 α -hydroxylase activity and thus is not believed to increase 1,25-(OH) $_2$ vitamin D levels (Table 2). This is relevant because 1,25-(OH) $_2$ vitamin D which is the normal physiologic mediator of calcium resorption activities in bone and intestine. Therefore, it is unusual to find elevated 1,25-(OH) $_2$ vitamin D levels at the same time as elevated PTHrP.

We believe this unexpected occurrence of both an elevated PTHrP and elevated 1,25-(OH) $_2$ vitamin D was only possible in this case because the patient took inordinately high doses of ergocalciferol for a prolonged period of time. It is well known that excessively high levels of 25-(OH) vitamin D or the metabolically active

Table 2: Expected versus observed lab findings in hypercalcemia of malignancy and hyperparathyroidism

	Intact PTH	PTHrP	1,25 Vit D	Calcium
Primary Hyperparathyroid	High	Low	High	High
Hypercalcemia of Malignancy	Low	High	Low	High
Current Case Report	Low	High	High	High

Abbreviations: PTH Parathyroid hormone, PTHrP Parathyroid Hormone Related Peptide

1,25-(OH)₂ vitamin D accentuate hypercalcemia. Vitamin D is fat soluble and thus has the potential to accumulate to toxic levels. Superphysiologic levels of 25-(OH) vitamin D in serum upregulate osteoclastic activity leading to increased calcium resorption from bones and an ensuing serum hypercalcemia. In vivo studies suggest that 25-(OH) vitamin D rather than 1,25-(OH)₂ vitamin D may be responsible for toxicity by competitively binding with vitamin D receptors [12, 13]. Finally, since vitamin D has a half-life of eight weeks in adipose tissue and 15 days in circulation, the hypercalcemia associated with vitamin D toxicity may continue for a few months until 25(OH) vitamin D levels return to normal. Treatment of vitamin D toxicity includes the supportive measures mentioned above primarily, but secondarily, it is reported that steroids reduce the extra-renal vitamin D 1 α -hydroxylase activity and therefore decrease the levels of circulating 1,25-(OH)₂ vitamin D. Other toxicities of vitamin D toxicity are nausea, nephrocalcinosis, vascular calcifications, nephrogenic diabetes insipidus, hypertension, and cardiac electrical abnormalities. Our patient only demonstrated nausea and hypertension.

CONCLUSION

Ultimately, this case report describes a rare treatment refractory case of hypercalcemia of malignancy (HCM) and novel treatment approaches to HCM. This case also highlights that vitamin D toxicity may cause paradoxical hypercalcemia. In the unique case of HCM driven by PTHrP and vitamin D toxicity, weekly dosing of denosumab may be safely utilized given close calcium monitoring. Aggressive hydration can be achieved to improve quality of life in carefully selected cases. Control of the underlying tumor remains a mainstay on HCM management. We recommend that vitamin D levels be routinely monitored during supplementation and that providers be made aware of the potential adverse outcomes in advanced cancer patients.

Author Contributions

Mohammed Athar Naeem – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

JoAnn Roslyn Phillips – Substantial contributions to conception and design, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Patrick Michael Dillon – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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