

UCLA

Proceedings of UCLA Health

Title

An Atypical Case of Humoral Hypercalcemia of Malignancy: Metastatic Cholangiocarcinoma

Permalink

<https://escholarship.org/uc/item/8761k1nf>

Journal

Proceedings of UCLA Health, 16(1)

Authors

Shah, Rena

Martinez, Dorothy

Publication Date

2012-02-16

CLINICAL VIGNETTE

An Atypical Case of Humoral Hypercalcemia of Malignancy: Metastatic Cholangiocarcinoma

Rena Shah, MD and Dorothy Martinez, M.D.

Introduction

Humoral hypercalcemia of malignancy (HHM) is a condition caused by systemic secretion of parathyroid hormone (PTH)-related protein (PTH-rP) by malignant tumors¹. PTH-rP is a protein that shares sequence homology at the amino-terminus with PTH and acts on PTH receptors. It has been found to have potent PTH-like bioactivity in vitro and in vivo². Thus, tumor production of PTH-rP results in changes that resemble those found in primary hyperparathyroidism such as hypercalcemia by promoting bone resorption and enhancing renal retention of calcium^{1,3}.

We report a case of an unusual source of HHM, followed by a discussion of PTH-rP and diagnosis and management of HHM.

Case Report

A 59-year-old male with a history of hypertension and diabetes mellitus presented to endocrinology complaining of one year of multiple symptoms, notable for a thirty pound weight loss, fatigue, lethargy, and vertigo. He had previously visited various physicians and been hospitalized at a local medical center one month prior, with similar complaints. During that hospitalization he was found to have an elevated serum calcium level of 14.4 mg/dL, and was treated with intravenous fluids and bisphosphonate therapy, and was discharged six days later once his calcium level had improved to 9.5 mg/dL. However, two weeks following discharge his symptoms gradually returned, prompting him to present to the UCLA endocrinology practice for further evaluation and management. The severe hypercalcemia raised concerns about malignancy, and subsequent lab

work revealed elevated calcium of 14.9 mg/dL, elevated corrected ionized calcium of 2.08 mmol/L, low end of normal PTH of 10 pg/mL, and markedly elevated PTH-rP of 116 pg/mL. Additionally, he had a normal serum protein electrophoresis, urine protein electrophoresis, and phosphorous level. He was admitted to the hospital for management and further evaluation of his severe hypercalcemia. He received intravenous normal saline, diuresis with furosemide, and a single infusion of 60mg of intravenous pamidronate. Given the concern of a PTH-rP secreting malignancy, further diagnostic tests were performed. CT scan of the abdomen/pelvis with intravenous and oral contrast revealed a heterogeneously enhancing left hepatic lobe lesion measuring 16 x 18 cm and a hypodense nonenhancing right hepatic lobe lesion 22 mm in diameter, with portal hypertension, hepatosplenomegaly, and ascites. Subsequently a fine needle aspiration of the left hepatic lobe mass was performed, and the biopsy revealed a well to moderately differentiated adenocarcinoma, with positive immunohistochemistry for cytokeratin 7. There were no abnormalities in hepatic panel or alpha-fetoprotein. CT scan of the chest revealed several subcentimeter mediastinal and pulmonary parenchymal nodules, suspicious for metastases from an extrathoracic primary carcinoma. These findings were most consistent metastatic adenocarcinoma, with the likely primary source being cholangiocarcinoma. The primary cholangiocarcinoma was likely secreting PTH-rP, and responsible for the patient's severe hypercalcemia. He was evaluated by Oncology and received a cycle of gemcitabine and cisplatin, with plans for continued chemotherapy at his local medical center.

Discussion

Malignancy associated hypercalcemia (MAH) is classified into four different types of processes.

These include local osteoclastic bone resorption, vitamin D mediated hypercalcemia, ectopic secretion of authentic PTH, and humoral hypercalcemia of malignancy². Humoral hypercalcemia of malignancy accounts for 80% of MAH. It results from the secretion of PTH-rP by tumors without the presence of primary hyperparathyroidism.

The concept of parathyroid hormone-like factors leading to hypercalcemia was first discussed in the 1940s by Albright after he was presented with a case of hypercalcemia as a result of renal cell carcinoma. Subsequently in the 1980s it was discovered that patients with hypercalcemia of malignancy had increased nephrogenous cAMP and increased adenylate cyclase activity in bone cells and renal membranes in the same manner as patients with elevated levels of PTH, however in the former subset they had an absence of elevated PTH. Later the active peptide responsible for this phenomenon was identified as PTH-rP¹.

PTH-rP is a peptide produced by tumors that shares sequence homology at the N-terminal sequence to PTH, and exerts its effects on calcium and phosphate homeostasis by binding and activating the type 1 PTH receptor. On the bone this effect is manifested in two ways. The immediate effect is the mobilization of calcium from skeletal stores that are readily available and in equilibrium with the extracellular fluid. Later there is also release of calcium and phosphate by activation of bone resorption. In the kidneys, the binding of PTH-rP to the type I PTH receptor stimulates synthesis of 1-alpha hydroxylase in the proximal tubules leading to increased conversion of calcidiol to calcitriol, and decreases activity of 24-hydroxylase that inactivates calcitriol².

Humoral hypercalcemia of malignancy has been reported in association with various malignancies such as squamous cell carcinoma of the lung, esophagus and cervix^{1,4}, renal cell carcinoma³, undifferentiated pancreatic cancer⁶, colorectal carcinoma⁷, thyroid follicular adenoma⁸, uterine leiomyosarcoma³, lymphomas, particularly HTLV associated, leukemias, bladder cancer, breast cancer, and ovarian cancer¹. In this paper we have reported a

malignancy, cholangiocarcinoma, that is not typically associated with humoral hypercalcemia.

Management of HHM should involve both antihypercalcemic therapy and antitumor therapy. Antitumor therapy is imperative, and the treatment is tailored specifically to underlying disease, tumor burden, and presence of metastases. With regard to treatment of hypercalcemia, management is similar across all cases regardless of underlying tumor. The development of hypercalcemia in malignancy is a poor prognostic sign, and can be fatal if left untreated. The management of MAH aims to reduce serum calcium levels and correct associated metabolic disturbances. Note that antihypercalcemic therapies are considered an interim measure, and do not have an ultimate implication on survival⁹. Generally, the neurologic and renal complications of hypercalcemia worsen with increasing levels and rate of ascent of serum calcium. The level of hypercalcemia can be classified as mild (serum calcium level of 10.5 to 11.9 mg/dL), moderate (12.0 to 13.9 mg/dL), and severe (14.0mg/dL or greater).

There are no formal guidelines for management of malignancy associated hypercalcemia, however there are general and specific measures that have shown to improve outcomes. General supportive measures include excluding calcium from parenteral feeding, discontinuation of oral calcium supplements, and discontinuation of medications that may independently result in hypercalcemia such as lithium, thiazides, and vitamin D¹. Hypercalcemia has a potent diuretic effect leading to volume depletion and dehydration. To protect against sodium loss, the kidney increases its tubular reabsorption which in turn leads to increased tubular reabsorption of calcium, further worsening hypercalcemia. Thus volume repletion is imperative for any cause of hypercalcemia. There are no formal guidelines on administration of intravenous hydration, however current practice is intravenous administration of 0.9% normal saline continuously at approximately 100 to 300 cc/hour. With intravenous hydration, serum calcium levels should decrease as there is decrease in concomitant reabsorption of sodium and calcium in both the proximal and distal renal tubule and there is enhanced urinary calcium excretion secondary to an increase in the glomerular filtration rate¹⁰. Once full hydration

has been achieved, the next step includes administration of loop diuretics, particularly furosemide, in conjunction with continued normal saline hydration. Loop diuretics increase the renal excretion of calcium by blocking calcium reabsorption in the loop of Henle. Thiazide diuretics should not be administered as they stimulate calcium reabsorption¹.

The most recognized medications for use in patients with malignancy associated hypercalcemia are the intravenous bisphosphonates. Bisphosphonates work by blocking osteoclastic bone resorption¹. Currently, in the United States, the agents of choice in treatment of mild to severe hypercalcemia are pamidronate and zoledronate. Bisphosphonates are given by single intravenous infusion over 15 minutes to 4 hours depending on the type of bisphosphonate¹⁰. Bisphosphonate therapy should be initiated immediately, as response requires two to four days and nadir of serum calcium is generally achieved within four to seven days after initiation of treatment. The majority of patients have a response for up to one to three weeks¹. In the case of an incomplete response, the infusion can be repeated after at least one week. There have only been a few head-to-head studies of bisphosphonates in the treatment of MAH. In an analysis of two randomized, controlled clinical trials, zoledronate was reported to be more effective than pamidronate in reducing serum calcium concentrations in patients with MAH and its effect appeared to last longer¹⁰.

There are a few other agents and treatments that can be employed to treat hypercalcemia. In life-threatening hypercalcemia high doses of parenteral calcitonin can be given in conjunction with the bisphosphonate every 6 to 8 hours during the first 24 hours¹⁰. Glucocorticoids and Mithramycin have also been infrequently used in cases when bisphosphonates are ineffective or contraindicated¹.

This case highlights the importance of evaluating PTH-rP levels when encountered with hypercalcemia associated with a suppressed PTH level. It additionally emphasizes the importance of evaluating for an occult malignancy in cases where PTH-rP levels are elevated from unknown etiology.

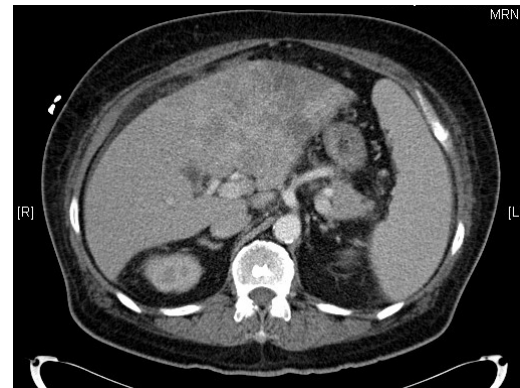


Figure 1: CT Abdomen/Pelvis with IV contrast demonstrate a heterogenous infiltrative mass replacing the left hepatic lobe with smaller ill-defined lesions in the right lobe. Ascites and splenomegaly also noted.

REFERENCES:

1. **Stewart AF.** Clinical practice. Hypercalcemia associated with cancer. *N Engl J Med.* 2005 Jan 27;352(4):373-9. Review. PubMed PMID: 15673803.
2. **Ratcliffe WA, Hutchesson AC, Bundred NJ, Ratcliffe JG.** Role of assays for parathyroid-hormone-related protein in investigation of hypercalcaemia. *Lancet.* 1992 Jan 18;339(8786):164-7. PubMed PMID: 1346019.
3. **Tang SJ, Geevarghese S, Saab S, Martinez D, Van Herle A, Wallace WD, Cortina GR, Dry S, Busuttil RW.** A parathyroid hormone-related protein-secreting metastatic epithelioid leiomyosarcoma. A case report and review of the literature. *Arch Pathol Lab Med.* 2003 Apr;127(4):e181-5. Review. PubMed PMID: 12683897.
4. **Gilmore JL, Gonterman RM, Menon K, Lorch G, Riese DJ 2nd, Robling A, Foley J.** Reconstitution of amphiregulin-epidermal growth factor receptor signaling in lung squamous cell carcinomas activates PTHrP gene expression and contributes to cancer-mediated diseases of the bone. *Mol Cancer Res.* 2009 Oct;7(10):1714-28. Epub 2009 Oct 13. PubMed PMID: 19825997; PubMed Central PMCID: PMC2784013.
5. **Soubrier C, Massfelder T.** Parathyroid hormone-related protein in human renal cell carcinoma. *Cancer Lett.* 2006 Aug 28;240(2):170-82. Epub 2005 Oct 11. Review. PubMed PMID: 16223565.
6. **Kakizaki S, Ohya N, Yoshinaga T, Higuchi T, Kitazawa R, Takayama H, Takagi H, Nagamine T, Mori M.** Undifferentiated pancreatic cancer associated with humoral hypercalcemia of malignancy. *Jpn J Clin Oncol.* 1998 Sep;28(9):563-6. Review. PubMed PMID: 9793031.
7. **Lortholary AH, Cadeau SD, Bertrand GM, Guerin-Meyer VI, Gamelin EC, Audran MJ.** Humoral hypercalcemia in patients with colorectal carcinoma: report of two cases and review of the literature. *Cancer.* 1999 Dec 1;86(11):2217-21. Review. PubMed PMID: 10590360.

8. **Hosokawa Y, Yamada Y, Iwamoto R, Kurokawa R, Ihara A, Yamamoto K, Sakaguchi K, Nakatsuka S, Minami Y, Matsuzawa Y.** Thyroid follicular adenoma producing parathyroid hormone-related protein with a normal serum calcium level. *Intern Med.* 2009;48(22):1957-61. Epub 2009 Nov 16. PubMed PMID: 19915296.
9. **Makras P, Papapoulos SE.** Medical treatment of hypercalcaemia. *Hormones (Athens).* 2009 Apr-Jun;8(2):83-95. Review. PubMed PMID: 19570736.
10. **Syed MA, Horwitz MJ, Tedesco MB, Garcia-Ocaña A, Wisniewski SR, Stewart AF.** Parathyroid hormone-related protein-(1--36) stimulates renal tubular calcium reabsorption in normal human volunteers: implications for the pathogenesis of humoral hypercalcemia of malignancy. *J Clin Endocrinol Metab.* 2001 Apr;86(4):1525-31. PubMed PMID: 11297578.

Submitted on February 16, 2012