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Hypercalcemia-Induced Hypokalemic Metabolic Alkalosis in a Multiple Myeloma Patient: The Risk of Furosemide Use

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Key Words
Hypercalcemia · Hypokalemic metabolic alkalosis · Furosemide

Abstract
Hypercalcemia is often seen in patients with malignancies, and in the past treatment for this has traditionally included loop diuretics. Clinically, patients with hypercalcemia frequently present with polyuria and volume contraction which may be further exacerbated by diuretic therapy. In the lab, hypercalcemia has been shown to activate the calcium-sensing receptor in the thick ascending limb of Henle and inactivate the 2 chloride sodium potassium co-transporter and induce a hypokalemic metabolic alkalosis, an effect similar to that of the loop diuretic furosemide. We now report what may well be the first clinical correlate of this laboratory finding in a patient who developed a hypokalemic metabolic alkalosis as a consequence of severe hypercalcemia due to multiple myeloma and whose metabolic derangement was corrected without the use of a loop diuretic which may have exacerbated the electrolyte abnormalities.

Introduction

Hypercalcemia is a frequent finding in patients with cancer and occurs in approximately 20–30% of patients [1]. The malignancies most commonly associated with hypercalcemia are breast, lung cancer and multiple myeloma. Hypercalcemia itself can contribute to other

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complications such as nausea, constipation, polyuria, polydipsia, nephrolithiasis and renal insufficiency. In addition, hypercalcemia is also associated with a metabolic alkalosis which may be due to buffers such as calcium carbonate and phosphates released from bone involved with metastatic disease. Hypokalemia is generally not seen with metastatic bone disease. In the laboratory, hypercalcemia activates the calcium-sensing receptor and has been shown to cause a hypokalemic metabolic alkalosis [2]. The mechanism by which this occurs is well worked out in vitro. The net effect is to inactivate the 2 chloride sodium potassium cotransporter in the thick ascending limb of Henle similar to the effect of furosemide. To date however, to our knowledge, there has been no clinical correlate of this laboratory finding. We report a case of multiple myeloma complicated by severe hypercalcemia associated with volume contraction, hypokalemia and a metabolic alkalosis likely associated with activation of the calcium-sensing receptor, perhaps the first clinical description of this laboratory finding.

Case Presentation

A 69-year-old African-American man presented with a 1-month history of progressive generalized weakness, fatigue and anorexia. The patient denied a history of constipation, polyuria or polydipsia, nausea or vomiting. He also did not ingest any nonsteroidal anti-inflammatory drugs. The patient was known to have longstanding hypertension with stage 2 chronic kidney disease due to hypertensive/vascular disease. He recently had sustained left rib fractures following a motor vehicle accident. His home medications included extended-release nifedipine, dutasteride, tamsulosin, ferrous sulfate and acetaminophen with codeine on a PRN basis. The patient was not on a diuretic. He did not take any over-the-counter medication. Specifically, he took no calcium-containing antacids.

On examination, the patient was alert and oriented ×3. Blood pressure was 120/70 mm Hg without any orthostatic changes demonstrable while on a saline infusion begun in the emergency room 1–2 h before. His home medications for his hypertension were discontinued on admission because of the observed relative hypotension. Cardiac, respiratory, abdominal and neurologic examinations were normal. There was no peripheral edema. Skin turgor was poor. The patient had reproducible left-sided chest pain associated with his recent motor vehicle accident. No other skeletal pain could be elicited on exam.

Initial blood work demonstrated a serum creatinine concentration of 433.2 μg/l, a serum calcium concentration of 4.38 mmol/l, a serum phosphorus concentration of 1.06 mmol/l and a normal serum albumin level of 40 g/l. His serum creatinine and calcium concentrations were noted to be 123.8 μg/l and 2.35 mmol/l, respectively, 5 months prior to hospitalization. In addition, the patient presented with a serum bicarbonate concentration of 32 mmol/l and a serum potassium concentration of 2.5 mmol/l. His hypokalemic metabolic alkalosis was confirmed by a venous blood gas.

The workup to elucidate the etiology of his hypercalcemia revealed his intact PTH level to be appropriately suppressed to 0.95 pmol/l (normal range: 1.06–6.9 pmol/l) and his PTH-related peptide level to be 27 ng/l (normal range: 14–27 ng/l). 25-hydroxy vitamin D and 1,25 vitamin D levels were 92.4 nmol/l (within normal range) and <19.2 pmol/l, respectively (low). The patient demonstrated 7 g of proteinuria by a urine protein-to-creatinine ratio. The urine analysis by dipstick, however, revealed only 1+ proteinuria. A serum protein electrophoresis revealed 2 abnormal bands within the beta and gamma regions, and assays for free light chains were elevated for both kappa and lambda and demonstrated an elevation of his kappa/lambda ratio.

A renal sonogram revealed normal-sized kidneys with bilateral renal cysts, and there was no evidence of hydronephrosis. A CT scan of the chest abdomen and pelvis without intravenous contrast was remarkable for numerous lytic lesions in the midsternum, in the right and left ribs, in the upper and lower thoracic and lumbar spine as well as in his scapulas. A subsequent bone marrow biopsy demonstrated a plasma cell dyscrasia with a CD38 monoclonal kappa plasma cell population.

The initial hypercalcemia, metabolic alkalosis and hypokalemia were treated with intravenous saline and potassium chloride supplementation. No intravenous furosemide was utilized. Within 3 days, his hypokalemic metabolic alkalosis totally resolved (serum potassium concentration 4.6 mmol/l and serum bicarbonate concentration 21 mmol/l). On day 5 of his hospitalization, chemotherapy was begun with bortezomib and dexamethasone. Although calcitonin and zoledronic acid were administered shortly after admission, he remained hypercalcemic until the 6th day of hospitalization. With continued therapy for his underlying malignancy, he remained normocalcemic, and his renal function returned to its baseline level 5 months after discharge.

Discussion

Malignancy-induced hypercalcemia occurs through at least 3 mechanisms. Hypercalcemia may be the result of osteolytic metastases with local release of cytokines, tumor secretion of parathyroid hormone-related peptide and tumor production of 1, 25-dihydroxy vitamin D [1, 3, 4]. Hypercalcemia in multiple myeloma may be the result of bone marrow infiltration and release of osteoclast-activating factors by the plasma cells [3]. This may be exacerbated by the attendant dehydration and renal involvement seen with hypercalcemia in myeloma.

Our patient had a normal parathyroid-related peptide level, nonelevated vitamin D levels and low normal phosphorus levels. With metastatic bony lesions, hyperphosphatemia is generally observed associated with the release of calcium phosphate and calcium carbonate from bone. This syndrome mimics the metabolic alkalosis seen with the calcium alkali syndrome [5]. Such a case was recently reported in a patient with multiple myeloma [6].

Of the above-described mechanisms responsible for hypercalcemia with malignancy, our patient does not appear to fit into any of the categories. Hormonal secretion was not the cause of hypercalcemia since parathyroid hormone-related peptide, 1,25-dihydroxy vitamin D and 25-hydroxy vitamin D were either normal or low. Although osteolytic lesions were present, the patient did not have hyperphosphatemia. The metabolic alkalosis observed with lytic lesions is secondary to release of calcium phosphorous and calcium carbonate from bone resulting in hyperphosphatemia. Our patient's phosphorus was low normal making the lytic lesions unlikely to be the cause of the observed metabolic alkalosis.

Interestingly, although there are sufficient laboratory data implicating hypercalcemia as a cause of hypokalemic metabolic alkalosis by activating the calcium-sensing receptor (see below), little attention has been given to the possibility that this occurs clinically. In our case, hypercalcemia, likely through its action on the renal calcium-sensing receptor, resulted in volume contraction, the generation of a hypokalemic, metabolic alkalosis and acute renal failure by the mechanism described below. Restoration of volume and potassium supplementation completely corrected the metabolic abnormality, and no furosemide was used to correct the associated hypercalcemia.

Calcium is a divalent ion and in its ionized form acts on cellular structures via the extracellular calcium-sensing receptor. The calcium-sensing receptor is an extracellular plasma

membrane-bound G-protein-coupled receptor that is present on the cell membrane of various tissues, including chief cells of the parathyroid glands, bone, kidney, bone marrow, gut and others. In vitro studies have demonstrated that small incremental increases in extracellular calcium concentrations can activate the calcium-sensing receptor and alter the function of the nephron and parathyroid glands so as to re-achieve normal serum calcium levels [2, 7, 8]. Hypercalcemia activates the calcium-sensing receptor on the basolateral surface of the thick ascending limb of Henle and generates arachidonic acid metabolites. These metabolites block the secretory potassium channel, and thus the 2 chloride sodium potassium co-transporter which requires luminal potassium to function fully is inhibited. This results in urinary losses of sodium, potassium, magnesium and calcium, and volume contraction due to an inability to concentrate urine. As a consequence of enhanced delivery of sodium to the distal convoluted tubule, under the effect of aldosterone which is elevated in the volume-contracted state, a hypokalemic metabolic alkalosis ensues similar to that seen in our patient. This effect is analogous to that seen with furosemide. To our knowledge, no such clinical correlation with hypercalcemia has been described to date. However, a drug-induced acquired Bartter-like syndrome has been associated with both gentamicin and amikacin administration in humans [9, 10]. Both of these drugs are polyvalent cationic molecules (+2) similar to calcium. The administration of both has been shown to cause a metabolic alkalosis and hypokalemia with polyuria. The authors suggest that activation of the calcium-sensing receptor in the thick ascending limb of Henle in these cases was responsible for the metabolic abnormalities similar to hypercalcemia and furosemide.

In summary, our case may well represent hypercalcemia causing a hypokalemic, metabolic alkalosis and volume contraction by activation of the calcium-sensing receptor. The patient responded to intravascular volume expansion and potassium supplementation with full correction of the metabolic alkalosis within 72 h. Classically, the initial treatment of hypercalcemia includes volume expansion and the use of furosemide to enhance urinary calcium excretion. Recently, the use of furosemide has been de-emphasized [11]. In fact, in the presence of hypercalcemia complicated by a metabolic alkalosis, in our opinion furosemide is contraindicated. The hypercalcemia already has presumably impaired the function of the 2 chloride sodium potassium co-transporter through its activation of the calcium-sensing receptor. Furosemide will further impair sodium reabsorption and volume contraction, and in fact may worsen the metabolic alkalosis and may result in cardiac arrhythmias, and thus its use is not warranted.

The development of new medications, particularly effective chemotherapeutic agents (bortezomib), and critical review of traditional therapies have changed the treatment approach to severe hypercalcemia, and there is now a limited role for aggressive isotonic fluid administration with furosemide [11]. The possibility of hypercalcemia itself causing metabolic alkalosis and hypokalemia needs to be seriously considered, and exacerbating this with furosemide needs to be meticulously avoided.

Statement of Ethics

The authors have no ethical conflicts to disclose.

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