Multiple myeloma with hypercalcemia and chloride resistant metabolic alkalosis

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Abstract:

This report describes a novel presentation of chloride resistant metabolic alkalosis in a patient with hypercalcemia related to Multiple Myeloma (MM). A 51 years old male with newly diagnosed MM presented with widespread skeletal involvement, calcium (Ca\(^{+2}\)) of 18 mg/dL, phosphorous (PO\(_4\)) of 6 mg/dL, serum bicarbonate (HCO\(_3\)) of 37 mEq/L, and serum creatinine (Cr) of 2.6 mg/dL. Other causes of metabolic alkalosis such as vomiting, diuretics, alkali ingestion, mineralocorticoid excess and hypokalemia were excluded. Hypercalcemia and metabolic alkalosis were only partially corrected after rehydration, calcitonin, and steroids. Subsequent treatment with zoledronic acid resulted in resolution of hypercalcemia and correction of metabolic alkalosis. The chloride resistant component of metabolic alkalosis was most likely related to extensive release of Ca\(^{+2}\), carbonate, and phosphate from bone by activated osteoclasts with inhibited osteoblastic activity. The additional reduction in glomerular filtration rate due to MM, contributed to a triad mimicking Calcium-Alkali syndrome.
Introduction:

Hypercalcemia has been associated with a number of acid-base abnormalities which vary depending on the etiology of the hypercalcemia (1). Chloride responsive forms of metabolic alkalosis are relatively common due to nausea and vomiting or the frequent use of loop diuretics (2, 3). Malignancy associated hypercalcemia has also been associated with chloride resistant forms of metabolic alkalosis secondary to excess aldosterone or cortisol production (adrenal tumor or ectopic ACTH production), use of exogenous alkali intake (classic milk-alkali syndrome), and/or severe hypokalemia (4-6). Release of bone related alkali has also been suggested as a potential mechanism for development of chloride resistant metabolic alkalosis in hypercalcemic patients (6-8).
Case Report:

A 51 years old previously healthy male presented with generalized fatigue, decreased appetite, night sweats and weight loss of 20 lbs (9 Kg) over one month and was found to have a chest wall mass. The patient reported constipation, but denied nausea, vomiting, polyuria or polydipsia. He denied any use of diuretics, non-steroidal anti-inflammatory drugs, anti-acids or calcium containing supplements. He denied alcohol or illicit drug use, but reported a 20 packs a year of smoking history. He was afebrile with HR of 80 beats per minute and BP 157/92 mmHg. Cardiac, respiratory, abdominal, and neurological examinations were normal. There was no peripheral edema and skin turgor was normal.

Laboratory evaluation at the time of presentation included a WBC of 16.6 ×10^9/L with 81% neutrophils, hematocrit of 34%, and platelet count of 307 × 10^9/L. On admission Ca^{2+} was 18.1 mg/dL, HCO_3^{-} 37 mEq/L and serum creatinine 2.6 mg/dL (creatinine was 1.3 mg/dl, HCO_3^{-} 33 mEq/L and Ca^{2+} 10.5 mg/dL 3 weeks before admission), sodium 142 mEq/L, potassium 4.3 mEq/L, chloride 96 mEq/L, and plasma anion gap 9 mEq/L. Urine chloride concentration before receiving any treatment was 46 mEq/L, plasma aldosterone 7.6 ng/dL (1-16 ng/dl), and plasma renin activity 0.42 ng/mL/hr (1.9 - 3.7 ng/mL/hour). Other laboratory values included normal TSH, suppressed PTH 10 pg/mL (normal values: 10 - 65 pg/mL), undetectable PTH-related peptide <0.3 pmol/L (normal value 0.0-1.5 pmol/L), low 25-hydroxycalciferol 13.4 ng/mL (normal values 8.9-46 ng/mL), low 1, 25 dihydroxy-Vit D < 5.0 pg/mL (normal 15.9-55.6 pg/mL), and Alkaline phosphatase of 172 U/L (normal 40-140 U/L).

Total protein concentration was 8.3 g/dL and albumin 4.1 g/dL. Quantitative immunoglobulin measurement demonstrated decreased concentrations of IgG, IgA, and IgM levels. Serum and urine immunofixation electrophoresis demonstrated the presence of monoclonal lambda light chain. Serum free light chain assay revealed free lambda light chain 3950 mg/L, compared to free kappa light chain assay at 23.60 mg/L. Urinalysis showed trace protein with no glucose,
specific gravity of 1.007, and urine PH of 5. Skeletal survey showed diffuse lytic lesions of the pelvis, sacrum, spine, scapula, sternum, and ribs. Histopathology with immunohistochemistry of biopsies of the chest wall mass and bone marrow revealed poorly differentiated lambda light chain restricted multiple myeloma with plasmablastic features with 8% plasma cells.

Hypercalcemia was initially treated aggressively by intravenous normal saline. Intravenous furosemide was administered twice daily for 48 hr. During the remainder of the 10 day hospitalization, the patient’s daily fluid intake (oral plus intravenous) was matched to his urine output. Body weight remained stable and there were no clinical signs of volume depletion. Additional treatments included calcitonin 200 mcg every 12 hours for 6 doses and high dose dexamethasone 40 mg for 3 doses. Serum Ca\(^{2+}\) partially corrected, stabilizing at 14.2 mg/dL and serum HCO\(_3\) remained elevated at 31 meq/L. He received zoledronic acid 3 mg intravenously one week after admission and was discharged with recommendations to maintain a normal salt intake and adequate fluid intake. The patient temporarily deferred initiation of further chemotherapy for personal reasons. On a follow up visit 10 days after the administration of zoledronic acid, laboratory evaluation included a serum Cr of 2.1 mg/dL, potassium 3.6 mEq/L, chloride 102 mEq/L, HCO\(_3\) 27 mEq/L and Ca\(^{2+}\) 7.5 mg/dl. 20 day later the patient was readmitted to initiate chemotherapy which included monthly high dose dexamethasone, oral thalidomide, and monthly zoledronic acid. Plasma bicarbonate remained 27 meq/l and calcium was 11.2 mg/dl and serum creatinine 3.0 mg/dl. Approximately 3 weeks later, he developed acute shortness of breath at home and expired on arrival to a local emergency department. Postmortem examination was not performed.

**Discussion:**

Although the most commonly associated acid base disorder with multiple myeloma is metabolic acidosis secondary to acute kidney injury and hyperchloremic normal anion gap metabolic acidosis secondary to proximal renal tubular acidosis secondary to Fanconi syndrome, the clinical and biochemical parameters in this patient are consistent with chloride
resistant metabolic alkalosis, the additional reduction in glomerular filtration rate (GFR) due to MM, contributed to a triad mimicking Calcium-Alkali syndrome (9,10). There was no history of vomiting or diuretic use, the urine chloride concentration prior to therapy was increased (46 meq/L), and administration of normal saline led to only partial correction of the metabolic alkalosis. The common etiologies of chloride resistant metabolic alkalosis such as excess cortisol or aldosterone leading to renal loss of hydrogen ions (11), contraction of extracellular volume (12), severe hypokalemia (13) and exogenous alkali administration (9,10,14) were not present. The extensive release of Ca^{2+} and buffering anions from bone (6-8) due to widespread lytic bone lesions, coupled with reduced GFR limiting bicarbonate excretion best explains the development of chloride resistant metabolic alkalosis. Treatment with the bisphosphonate, zoledronic acid, resulted in inhibition of bone resorption via its actions on osteoclasts with reduced release of calcium and anions from bone leading to correction of both hypercalcemia and metabolic alkalosis.

Chloride responsive metabolic alkalosis due to hydrogen ion loss from the gastrointestinal tract or the use of diuretics has been the most common form of metabolic alkalosis associated with malignancy (1,3,15). Milionis et al studied acid-base abnormalities associated with 76 hypercalcemic hospitalized patients. Primary hyperparathyroidism and malignancy were the most common causes of hypercalcemia. In this study, 9 patients had metabolic alkalosis. All had malignancy; 2/9 had diuretic induced alkalosis, while 7/9 had prerenal azotemia, mild hypokalemia, and reduced urinary chloride (<20 mmol/L), features consistent with chloride responsive metabolic alkalosis (1). The response to therapy was not reported.

Heinemann described 20 patients with hypercalcemic secondary to malignancy who had mild to moderate metabolic alkalosis that could not be attributed to commonly recognized causes (6); 19 of the 20 patients had metastatic bone lesions (breast cancer, lung cancer, or multiple myeloma). Metabolic alkalosis improved following correction of the hypercalcemia in 7
of the 20 patients. The authors concluded that the metabolic alkalosis in these hypercalcemic patients was caused by the increased release of bone buffers occurring as a consequence of enhanced bone turnover and breakdown associated with the underlying malignancy related bone lesions.

Multiple myeloma is associated with enhanced osteolysis via osteoclasts activating factors now recognized as macrophage inhibitory protein-1 alpha (MIP-1 protein) (16). Myeloma cells also inhibit osteoblastogenesis by blocking Runx2 activity in mesenchymal and osteoprogenitor cells through the direct cell-to-cell contact with the involvement of VLA-4–VCAM-1 interaction (17). The simultaneous activation of osteoclast bone resorption and inhibition of osteoblast bone formation, which occurs in multiple myeloma, results in release of calcium, phosphorous and carbonate from the bone. The subsequent metabolism of carbonate results in bicarbonate production. Multiple myeloma often results in renal insufficiency due to effects of hypercalcemia, cast nephropathy, or direct toxic effects of light chains, which further impairs excretion of calcium and alkali released from the bone. These alterations likely explain the development of features which mimic the Calcium-Alkali syndrome with a triad of hypercalcemia, chloride resistant metabolic alkalosis, and renal insufficiency in the absence of exogenous intake in our patient who had extreme hypercalcemia (18.1 mg/dl), a very high tumor burden, and extensive skeletal involvement.

Previous studies have shown significant differences in acid base and electrolyte disorders between hypercalcemic patients due to hyperparathyroidism, as compared to patients with neoplasia. Metabolic acidosis, a high serum chloride to phosphorus ratio and reduced plasma anion gap have been described in patients with hyperparathyroidism (18, 19). Hyperparathyroidism results in activation of osteoclasts via activation of adenylate cyclase activity (20). The osteoclastic activation is also associated with osteoblast activation resulting in new bone formation, which limits excessive bone alkali release to the circulation. Humoral hypercalcemia of malignancy can be caused by multiple mechanisms, including: a) local
osteolytic effects mediated by cytokines or chemokines b) secretion of PTH-related peptide, via enhanced bone resorption and renal retention of calcium via effects similar to PTH c) via secretion of active forms of Vitamin D (lymphomas) which cause enhanced intestinal absorption of calcium and d) rarely by ectopic production of PTH (21, 22).

In this novel case, the source of calcium and carbonate was endogenously produced from the widespread skeletal involvement in this patient with multiple myeloma with extensive release of Ca\(^{2+}\) and bone buffers due to activated osteoclasts with concomitant inhibition of osteoblastic activity, contributing to the development of chloride resistant metabolic alkalosis and hypercalcemia. The additional reduction in GFR secondary to multiple myeloma contributed to a triad mimicking the Calcium-Alkali syndrome. The prompt correction of hypocalcemia and metabolic alkalosis by osteoclast inhibition with bisphosphonate therapy only supports our theory.

References:


