

CASE REPORTS

Hypercalcemia due to milk alkali syndrome: An emerging cause of hypercalcemia: A case report and review of literature

Yadav Pandey*¹, Krishna Prasad Joshi¹, Priya Priyambada², Anmol Chaudhary³

¹Department of Internal Medicine, University of Arkansas for Medical Sciences, Little Rock, AR, USA

²Department of Family and Preventive Medicine, University of Arkansas for Medical Sciences, Little Rock, AR, USA

³Department of Internal Medicine, Kathmandu Medical College, Nepal

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ABSTRACT

Introduction: Hypercalcemia is relatively common in clinical practice. Primary hyperparathyroidism and malignancy accounts for more than 90 percent of all cases of hypercalcemia. Milk alkali syndrome which is hypercalcemia classically caused by ingestion of large amount of calcium and absorbable alkali which was once virtually disappeared as a cause of hypercalcemia has emerged as a third leading cause of hypercalcemia. We present a case of hypercalcemia secondary to ingestion of calcium carbonate tablets resulting in milk alkali syndrome.

Case presentation: Patient is a 45-year-old female with history of gastroesophageal reflux disease came to the emergency department with complaints of dizziness, constipation, fatigue and confusion for 3 weeks. She was hypotensive to 83/53 mmHg at arrival. Significant laboratory results were - Potassium of 2.2 mmol/L (3.5-5.1 mmol/L), chloride 73 mmol/L (98-107 mmol/L), Bicarbonate 50 mmol/L (22-29 mmol/L), Blood urea 22 mg/dl (9.8-20.1 mg/dl), Cr 1.4 mg/dl (0.5-1.0 mg/dl), total calcium of 16.6 mg/dl (9-11 mg/dl), ionized calcium 2.02 mmol/L (1.15-1.33 mmol/L), PTH was low to 8.9 pg/ml (10-65 pg/ml). Arterial blood gas showed metabolic alkalosis. Extensive evaluation to find the cause of hypercalcemia was negative. Detailed history after initial stabilization, revealed that she had been taking 10 tablets of calcium carbonate tablets per day and 1 glass of milk daily for reflux symptoms for the last eight weeks. Based on the history and after ruling out all the other serious causes, diagnosis of milk alkali syndrome was made and patient was discharged with proton pump inhibitor with advice to avoid calcium carbonate. Her hypercalcemia responded well to fluid resuscitation.

Conclusions: Milk alkali syndrome once a rare cause of hypercalcemia has emerged as a third leading cause of hypercalcemia in completely different scenario. It is important to evaluate the patient with proper history including the use of over the counter calcium supplements to determine the etiology of hypercalcemia. Our case highlights the importance of proper history taking in the evaluation of hypercalcemia and that not all the cause of severe hypercalcemia is secondary to malignancy.

Key Words: Hypercalcemia, Milk-alkali syndrome, Hyperparathyroidism

*Correspondence: Yadav Pandey; Email: pandey.ydv@gmail.com; Address: Department of Internal Medicine, University of Arkansas for Medical Sciences, Little Rock, AR, USA.

1. INTRODUCTION

Hypercalcemia is relatively common in clinical practice. Primary hyperparathyroidism and malignancy accounts for more than 90 percent of all cases of hypercalcemia.^[1-3] Milk alkali syndrome which is hypercalcemia classically caused by ingestion of large amount of calcium and absorbable alkali which was once virtually disappeared as a cause of hypercalcemia has emerged as a third leading cause of hypercalcemia.^[4,5] We present a case of hypercalcemia secondary to ingestion of calcium carbonate tablets resulting in milk alkali syndrome.

2. CASE PRESENTATION

Patient is a 45-year-old female with history of gastroesophageal reflux disease came to the emergency department with complaints of dizziness for 3 weeks. History was positive for constipation, fatigue and confusion. She reported loss of appetite and nausea with occasional vomiting for 1 week. She also reported increased frequency of urination and felt like she is dehydrated. She denied any fever, headache, cough, chest pain or shortness of breath. Exam was positive for mild confusion but cardiovascular, respiratory and abdominal examinations were normal. She was hypotensive to 83/53 mmHg at arrival which got better after intravenous fluid boluses. Laboratory results showed normal blood counts. Basic metabolic panel showed sodium 137 mmol/L (136-145 mmol/L), Potassium of 2.2 mmol/L (3.5-5.1 mmol/L), chloride 73 mmol/L (98-107 mmol/L), Bicarbonate 50 mmol/L (22-29 mmol/L), Blood urea 22 mg/dl (9.8-20.1 mg/dl), Cr 1.4 mg/dl (0.5-1.0 mg/dl), total calcium of 16.6 mg/dl (9-11 mg/dl), ionized calcium 2.02 mmol/L (1.15-1.33 mmol/L), serum albumin was 4.4 g/dl (3.5-5.5 g/dl), Mg 1.3 mg/dl (1.7-2.2 mg/dl), Phosphorus 2.4 mg/dl (2.5-4.5 mg/dl), blood sugar 94 mg/dl. Lactate was 0.9 mmol/L, Arterial blood gas showed metabolic alkalosis with PH of 7.67, PCO₂ 49, PO₂ 101 with HCO₃ 56.5. For evaluation of hypercalcemia, PTH was measured and was found to be low to 8.9 pg/ml (10-65 pg/ml). TSH was normal. Urine drug screen was negative. PTH related peptide (PTHrP) was normal to 0.5 pg/ml. 24-hydroxy vitamin D was low to 24.5. 1,25 dihydroxy vitamin D was low to < 5. CT head done for confusion was negative for acute intracranial lesions and CT chest showed no suspicion of lung mass or sarcoidosis. Serum electrophoresis for light chains was negative. She was initially treated with fluid resuscitation and diuretics after stabilization of blood pressure. Detailed history after initial stabilization, revealed that she had been taking 10 tablets of calcium carbonate tablets per day and 1 glass of milk daily for reflux symptoms for last eight weeks as she was told by a friend that over the counter

calcium carbonate is safe and effective for reflux symptoms. Patient was not following anyone as her primary care physician and was not aware of any abnormal labs values. Based on the history and after ruling out all the other serious causes, diagnosis of milk alkali syndrome was made and patient was discharged with proton pump inhibitor with advice to avoid calcium carbonate. Her hypercalcemia responded well to fluid resuscitation.

3. DISCUSSION

Malignancy and primary hypoparathyroidism are the two major causes of hypercalcemia.^[4] It is often not difficult to differentiate between these two, as malignancy is often evident by the time it causes hypercalcemia. Calcium level in malignancy is much higher than in primary hypoparathyroidism. Malignancy is the most common cause of hypercalcemia in the inpatient setting occurring in the patients with both solid tumors and hematologic malignancies.^[6] There are 3 major mechanisms for hypercalcemia of malignancy – production of parathyroid hormone related protein (PTHrP), osteolytic metastasis resulting in release of cytokines locally and production of calcitriol by tumor cells.^[7] In primary hyperparathyroidism patient, often present with asymptomatic hypercalcemia and elevated calcium as an incidental finding.^[8] Hypercalcemia in primary hyperparathyroidism is due to parathyroid hormone-mediated activation of osteoclast leading to bone resorption.

Milk alkali syndrome consisting of a classic triad of hypercalcemia, metabolic alkalosis and acute kidney injury has emerged as a third common cause of hypercalcemia.^[4] Historically, milk alkali syndrome was caused by the use of milk and sodium bicarbonate for the treatment of peptic ulcer disease.^[9,10] The occurrence of milk-alkali syndrome had dramatically reduced with the use of more effective non-alkali therapies for peptic ulcer disease like proton pump inhibitors and H₂ blockers.^[11] However, recently the incidence has increased secondary to the use of calcium carbonate to minimize secondary hyperphosphatemia in patients with chronic kidney disease and use of calcium therapy for prevention as well as treatment of osteoporosis.^[4,5] In addition, due to the easy availability of the over the counter calcium containing antacids, incidence of calcium alkali syndrome has increased. Due to change in cause and epidemiology over time, many authors prefer to use the terminology calcium-alkali syndrome instead of milk-alkali syndrome.^[12] Currently, almost 12% of the hypercalcemia is contributed to milk-alkali syndrome.^[5]

Although milk alkali syndrome is caused by ingestion of calcium with absorbable alkali, only few patients taking large amount of calcium carbonate develop sustained hyper-

calcemia and metabolic alkalosis with kidney injury.^[9,13] Various mechanisms play important role to prevent hypercalcemia in patients with excessive intake. Reduced calcium absorption due to suppressed vitamin D^[14] and buffering of excess calcium by bone^[15] are the important ones. It is unclear why only some individuals are affected by excessive intake. Such individuals tend to have increased absorption and failure in suppression of calcitriol in response to hypercalcemia.^[16] Age plays an important role; older individuals tend to have a reduced bone-buffering capacity which put them at higher risk for hypercalcemia.^[17] Hypercalcemia in milk alkali syndrome tends to maintain itself by volume depletion by diuresis and natriuresis; decreased GFR leading to decreased filtration of calcium via kidney and increased renal

reabsorption of calcium due to metabolic alkalosis^[18] (see Figure 1). Historically, milk alkali syndrome seen during the treatment of peptic ulcer with Sippy regimen caused hyperphosphatemia due to ingestion of phosphorus rich milk. However, ingestion of calcium carbonate without milk for treatment of osteoporosis or self-treatment of dyspepsia with cause low to normal hypophosphatemia due phosphate binding property of calcium carbonate and absence of phosphate loading.^[4,18] Hypophosphatemia is more common in elderly patient probably secondary to reduced ingestion of dietary phosphorus.^[19] Interestingly in our case, patient was taking one glass of milk every day which might have prevented her from developing severe hypophosphatemia.

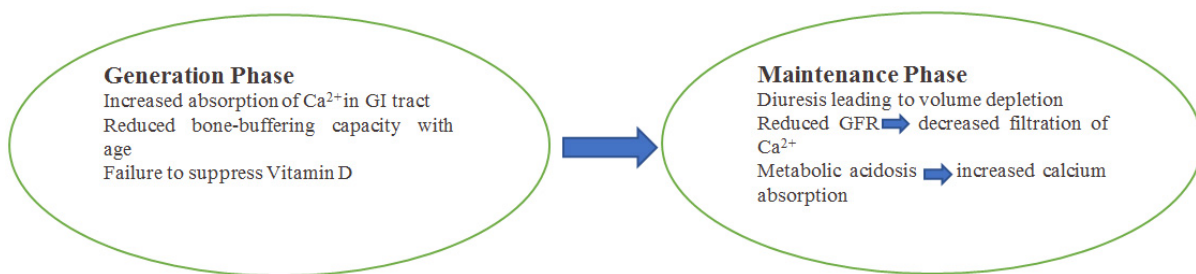


Figure 1. Mechanism showing generation and maintenance of hypercalcemia in milk alkali syndrome^[18]

Clinical manifestation of hypercalcemia can range from asymptomatic incidental finding to obtundation and coma.^[20] Depending upon the level of serum calcium and chronicity, patient can present with the milder symptoms like fatigue, constipation, nausea to more severe symptoms like polyuria, polydipsia, dehydration, anorexia, muscle weakness and confusion.^[20,21] Neuropsychiatric disturbances like depression, anxiety and cognitive dysfunction is also common in patient with chronic hypercalcemia. In rapidly progressing hypercalcemia, patient can present with more severe symptoms like lethargy, altered sensorium, stupor and coma.^[4,21] Similarly, in hypercalcemia due to milk alkali syndrome, patients are often asymptomatic and abnormal lab finding of elevated calcium, alkalosis and renal dysfunction is an incidental finding. Other common lab findings are hypophosphatemia secondary to phosphate-binding property of calcium carbonate and hypomagnesemia due to hypercalcemia-induced inhibition of magnesium reabsorption by renal tubules.^[5] Reduced PTH level helps to distinguish the milk alkali syndrome from primary hyperparathyroidism.^[16]

Stopping the offending agent along with hydration with isotonic saline and furosemide is the mainstay of treatment of

milk alkali syndrome.^[22] In milk alkali syndrome, there is chronically suppressed PTH due to chronic hypercalcemia which is an important point to consider during treatment of hypercalcemia in milk alkali syndrome. As a result, hypocalcemia is often common after treatment.^[4] For the same reason, bisphosphonates should be avoided in the treatment of hypercalcemia, which can result in prolonged suppression of serum calcium and exacerbate hypocalcemia.^[5]

4. CONCLUSION

Milk alkali syndrome once a rare cause of hypercalcemia has emerged as a third leading cause of hypercalcemia in completely different scenario. It is important to evaluate the patient with proper history including the use of over the counter calcium supplements to determine the etiology of hypercalcemia. Use of more effective proton pump inhibitor and H2 blockers helps to reduce the risk of hypercalcemia. Our case highlights the importance of proper history taking in the evaluation of hypercalcemia and not all the cause of severe hypercalcemia is secondary to malignancy.

CONFLICTS OF INTEREST DISCLOSURE

The authors declare no conflicts of interest.

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