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Milk Alkali Syndrome

Darshan B. Shah, George Liji

ABSTRACT

Milk-alkali syndrome consists of the triad of hypercalcemia, metabolic alkalosis, and renal insufficiency associated with the ingestion of large amounts of calcium and absorbable alkali. There has been a resurgence of this disorder, as it now accounts for up to 12 percent of cases, making it the third leading cause of hypercalcemia behind primary hyperparathyroidism and malignancy. We present a case report of a 38-year-old male with ingestion of large amounts of calcium carbonate resulting into milk-alkali syndrome and its complications. Avoid excessive amounts of calcium carbonate ingestion.

Keywords: Calcium carbonate, Milk alkali syndrome

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Darshan B. Shah[1], George Liji[2]

Affiliations: [1]Hospitalist in Polk county, Florida. Bartow Regional Medical Centre and Lakeland Regional Medical Centre, Assistant Professor at University of Central Florida College of Medicine, Florida, US; [2]Primary Care Physician working at Baycare Medical Group in Plant City, Florida, US.

Corresponding Author: Dr. Darshan B. Shah, 1799 Altavista Circle, Lakeland, Florida 33810, US; Email: darshans2000@gmail.com

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INTRODUCTION

Milk-alkali syndrome is a triad of hypercalcemia, metabolic alkalosis, and renal insufficiency. This is associated with the ingestion of large amounts of calcium and absorbable alkali. Since the advent of new treatment modalities for peptic ulcer disease, the incidence of milk alkali syndrome has decreased. By 1985, the milk-alkali syndrome was considered the cause of less than one percent of cases of hypercalcemia. However, there has been a resurgence of this disorder, as it now accounts for up to 12 percent of cases, making it the third leading cause of hypercalcemia behind primary hyperparathyroidism and malignancy.

CASE REPORT

A 38-year-old Caucasian male with history significant for GERD, hiatal hernia & eczema presents with chief complaint of altered mental status. His symptoms started a week ago when he had nausea, vomiting, abdominal pain, diarrhea, low-grade fever, weakness and decreased oral intake. Most of his symptoms resolved but he continued to have myalgias, abdominal pain, weakness and fatigue. He attributed this to his new job as night time security officer. Meanwhile he also developed bilateral lower extremity pain, cramps, constipation, tremors and headaches. He also reported 14 pounds unintentional weight loss in two weeks. He denied any history of sick contact, recent travel or previous similar episodes. His home medications were Tylenol and tums (calcium carbonate). He is a social drinker, he has quit smoking five months ago and denied any recreational drug use. Being an adopted child, he was unsure about his family history.

On physical examination, temperature was 96.9 F, heart rate was 95 bpm, blood pressure was 202/104 mm Hg, respiratory rate was 20 saturating 96% on room air.

Patient was awake, alert and oriented, was in mild distress and had sluggish verbal responses. His mucous membranes were dry. Abdominal examination revealed diffuse tenderness on deep palpation. Bilateral calf

tenderness was present. Bilateral lower extremity power decreased to 2/5. Rest of the physical examination was unremarkable. Initial diagnostic work up and results are as shown in (Table 1 and 2). EKG showed prolonged T waves with a normal QT interval. CT head was normal. The patient was admitted to the intensive care unit for his hypertensive urgency and electrolyte imbalances. Further history was elicited on his tums (calcium carbonate) consumption once hypercalcemia was detected. Laboratory workup for hypercalcemia was done as outlined in Table 3. He admitted ingestion of 10-15 gms of tums every day. On the basis of the laboratory findings and clinical picture, Milk-Alkali syndrome was suspected and patient was started on aggressive hydration.

Case outcome

Our patient was treated with aggressive IV hydration. Calcium carbonate was stopped. He received hemodialysis twice during his hospital stay of seven days. His symptoms improved.

Trends of his serum calcium, creatinine, bicarbonate and phosphorus are as follows (Table 4).

The patient was counseled on the nature of his condition, and he was advised to avoid taking excessive amounts of calcium. In the following months, his serum creatinine normalized, and he remained asymptomatic.

Table 1: Laboratory data

Labs	Results	Reference range
Hemoglobin	12	13.7–17.5 g/dl
Hematocrit	34	40.1–51.0 %
WBC	11.20	3.60–10.30x10^9/l
Platelets	330	140–420x10^9/l
Sodium	129	136–145 mEq/L
Potassium	2.2	3.5–5.1 mEq/L
Chloride	81	98–107 mEq/L
Bicarbonate	37	24–32 mEq/L
BUN	97	7–21 mg/dl
Creatinine	6.4	0.7–1.2 mg/dl
Glucose	200	70–105 mg/dl
Calcium	19.9	8.7–10.6 mg/dl
Magnesium	1.7	1.2–2.2 mg/dl
Phosphorus	1.8	2.7–4.5 mg/dl
Protein	6.2	6.3–8.2 g/dl
Albumin	3.6	4.0–5.0 g/dl
Bilirubin	0.6	0.2–1.3 mg/dl
AST	47	10–34 U/L
ALT	32	10–34 U/L
Alkaline Phosphatase	124	40–129 U/L
TSH	0.38	0.34–5.60 µu/ml
Cardiac Enzymes	Normal	

Table 2: Arterial blood gas results

Labs	Results	Reference range
pH	7.51	7.35–7.45
paCO2	46.3	35–45 mm Hg
pO2	71.1	70–95 mm Hg
HCO3	36	20–28 mEq/L

Table 3: Labs done to evaluate the cause of Hypercalcemia

Labs	Results	Reference range
PTHrP	< 2.1	0.02–4.0 pmol/L
Vitamin D 1,25	8.6	15.9–75.6 ng/ml
PTH	6.4	12–88 pg/ml
ACTH	49	6–48 ng/l
Cortisol Random	12.9	10–20 mcg/dl
Vitamin D 25	14.4	32–100 ng/ml
Urine calcium	353.8	100–300 mg/day
Urine Electrophoresis	Normal	
Serum Electrophoresis	Normal	
Urine culture	Negative	
Blood Culture	Negative	

DISCUSSION

Milk-alkali syndrome is a triad of hypercalcemia, metabolic alkalosis, and renal insufficiency. This is associated with the ingestion of large amounts of calcium and absorbable alkali. Since the advent of new treatment modalities for peptic ulcer disease, the incidence of milk alkali syndrome has decreased. By 1985, the milk-alkali syndrome was considered the cause of less than one percent of cases of hypercalcemia [1]. However, there has been a resurgence of this disorder, as it now accounts for up to 12 percent of cases, making it the third leading cause of hypercalcemia behind primary hyperparathyroidism and malignancy [2, 3]. In 1949, Burnett et al. [4] reported a “milk and alkali syndrome” in six male patients treated with milk and sodium bicarbonate for peptic ulcer disease. All previously reported cases of Milk Alkali syndrome were reexamined by Punsar and Somer [5] in 1963. They classified Milk alkali syndrome into 2 types: Cope syndrome (acute) and Burnett syndrome (chronic).

The proximate cause of the milk alkali syndrome is the ingestion of large amounts of calcium in conjunction with absorbable alkali. It is probable that normal renal function and suppression of calcitriol production allows maintenance of calcium and acid-base balance in most individuals exposed to large doses of calcium and alkali. Increased intake of calcium results in decreased 25-hydroxylation of vitamin D by the kidneys, which leads to a marked decrease of fractional calcium absorption in the small intestine. Calcium intakes exceeding 4 grams per day are necessary to achieve normal levels in the absence of calcitriol. However, net calcium absorption increases markedly when intake is increased to 10

Table 4: Daily trends of relevant lab values

Labs	Range	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
Calcium	8.7–10.6	19.9	17.9	11.0	11.1	10.5	9.1	8.8	8.1
Creatinine	0.7–1.2	6.4	6.0	4.1	2.7	3.2	3.4	3.3	2.9
Bicarbonate	24–32	37	35	26	29	25	21	21	21
Phosphorus	2.7–4.5	1.8	2.2	1.6	0.8	1.7	3.1	3.4	4.1

to 15 grams per day. In addition, metabolic alkalosis directly stimulates tubular calcium transport [6]. This combination frequently leads to an increase in plasma calcium concentration [7].

Alkalosis reduces calcium excretion by increasing its tubular reabsorption [6, 8], which is PTH independent [6]. Hypercalcemia impairs the kidneys' ability to excrete excess bicarbonate, which in predisposed individuals may lead to severe hypercalcemia and renal failure. The increased serum calcium level causes further afferent arteriole constriction and decrease in the glomerular filtration rate [9, 10].

Classical presentation — three clinical syndromes have been recognized [11].

Acute – Acute or toxemic form occurred after approximately one week of treatment. The symptoms were those of acute hypercalcemia, and included nausea, vomiting, weakness, and mental changes with psychosis or depressed sensorium. There was also severe metabolic alkalosis, a normal to elevated plasma phosphate concentration, and acute renal insufficiency. Withdrawal of milk and alkali led to rapid relief of symptoms and the return of normal renal function.

Subacute or intermediate — In the subacute form, patients were usually seen during therapy with milk and alkali that had been taken intermittently for years [5]. Affected patients had symptoms of both acute and chronic hypercalcemia and responded to medication withdrawal with gradual improvement. Renal function remained mildly impaired in some cases.

Chronic — In the chronic form patients presented after a long history of high milk-alkali intake with symptoms of chronic hypercalcemia, such as polyuria, polydipsia, muscle aches, and pruritus [4, 12, 13]. Frequently, there was evidence of metastatic calcifications, including band keratopathy and nephrocalcinosis. Laboratory abnormalities were similar to those in the acute syndrome, but the response to withdrawal of milk and alkali was quite different. The muscle aches and pruritus improved slowly as the plasma calcium concentration slowly normalized. However, there was usually minimal or no improvement in renal function, as many patients continued to have chronic renal failure.

Modern presentation — Since 1990, approximately 40 patients have been reported [2, 14, 15]. Fifty-five percent were women, and calcium carbonate was the predominant source of calcium and alkali intake in all patients, supplemented with milk in 43 percent. Reported intakes of calcium carbonate range from 2.5 - 20 grams per day.

Criteria for diagnosis of milk alkali syndrome include hypercalcemia, relative or absolute metabolic alkalosis at identification of hypercalcemia: serum bicarbonate > 24 mmol/l, renal insufficiency (serum creatinine concentration > 1.3 mg/dl), history of consumption of calcium and absorbable alkali and absence of known malignancy or other identifiable cause for the above-mentioned metabolic abnormalities.

Any of the following findings was considered an additional supportive criterion:

1. Suppressed or low-normal serum concentrations of PTH, PTH related peptide and 1,25-dihydroxyvitamin D
2. Normal corrected serum calcium concentration at follow-up, at least 4 months after decreasing the dose or discontinuing intake of calcium and alkali.
3. Recurrence of the metabolic picture with resumption of intake of calcium and absorbable alkali.

The differential diagnosis includes parathyroid disorder, malignancy, vitamin D related disorders, addisons disease and inflammatory disorders.

Parathyroid disorder – A normal or high intact PTH levels suggest primary hyperparathyroidism. Our patient's intact parathyroid hormone levels were low which excluded primary hyperparathyroidism, which is the most common cause of hypercalcemia.

Malignancy - Neoplasms commonly associated with hypercalcemia include squamous cell cancers of the upper respiratory-digestive tract, breast cancer, myeloma, and renal cancers [16]. PTH-related peptide (PTHrP) is the principal mediator in hypercalcemiaassociated with solid tumor [17]. These neoplasms are typically large, advanced, andquite evident. Another common cause of neoplastic hypercalcemia is plasma cell disease. Patients with plasma cell disease frequently have significant skeletal involvement, with classic lytic lesions. Patient's total protein, alkaline phosphatase, urine and serum protein electrophoresis, radiographs, renal ultrasound and PTHrP were normal which ruled out malignancy.

Vitamin D related disorders – Vitamin D is a steroid hormone that is obtained through the diet or produced by the action of sunlight on vitamin D precursors in the skin. Calcitriol, the active form of vitamin D, is derived from successive hydroxylation of the precursor cholecalciferol, first in the liver (25-hydroxylation), then in the kidneys (1-hydroxylation). Adequate vitamin D is necessary for bone formation. However, the principal target for vitamin D is the gut, where it increases the absorption

of calcium and phosphate. Thus, in vitamin D-mediated hypercalcemia, vitamin D and serum phosphate levels tend to be high. Our patients 1,25 vitamin D, 25 OH vitamin D andphosphorus levels were low excluding vitamin D related causes.

Others - Normal ACTH, cortisol, TSH ruled out other endocrine causes. Blood and Urine cultures along with normal ESR and CRP excluded inflammatory/infectious causes.

Given the constellation of symptoms, laboratory findings and excluding several other potential causes, a diagnosis of Milk Alkali Syndrome was made on our patient.

Daily calcium requirement is 1000-1300 mg. Tolerable upper intake level is 2000 mg. Lower doses of calcium may still cause hypercalcemia and MAS in predisposed individuals. Most cases of Hypercalcemia resolve with hydration, supportive management and removal of the offending agent. Acute form resolves in a short period of 2-3 days, but symptomatic improvement in chronic form takes longer. Hemodialysis is occasionally required in refractory cases. Renal failure improves but does not always resolve completely. Calciuresis can be augmented by using loop diuretics. Administering bisphosphonates to patients with MAS has been reported [3], but no data are available to support the theory that bisphosphonates change outcome. Hypercalcemia usually resolves within several days, but serum calcium levels can be elevated up to 6 months [18]. Symptomatic temporary hypocalcemia may require replacement therapy [2] which is due to slow recovery of the serum PTH level.

CONCLUSION

Increased awareness of osteoporosis, routine calcium supplements for its prevention along with use of calcium carbonate for peptic ulcer disease has caused a resurgence of milk alkali syndrome. Treatment is supportive and involves hydration and removal of the offending agents. Physicians and the public need to be aware of the potential adversarial outcomes of consuming excessive amounts of calcium carbonate.

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Author Contributions

Darshan B. Shah – 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

George Liji – 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 of Submission

The corresponding author is the guarantor of submission.

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Conflict of Interest
Authors declare no conflict of interest.

Data Availability
All relevant data are within the paper and its Supporting Information files.