Calcium Carbonate (Tums)-Associated Milk-Alkali Syndrome as a Cause of Altered Mental Status in the Emergency Department: A Case Report

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Case Report

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Abstract

Background:

Milk-alkali syndrome (MAS) resulting in hypercalcemic crisis represents a life-threatening medical emergency in the setting of excessive calcium and absorbable alkali ingestion. While an uncommon cause of altered mental status and acute renal failure in the emergency department, emergency medicine clinicians should be aware of this syndrome due to significant morbidity and mortality if left undiagnosed.

Case presentation:

A 63-year-old woman with history of familial hypoparathyroidism presented to our emergency department with worsening confusion, slurred speech, generalized weakness, and failure to thrive over the course of one month. Review of systems was positive for tachypnea, polydipsia, diffuse musculoskeletal pain, dehydration, poor oral intake, nausea with nonbilious nonbloody emesis, and severe fatigue. Family reported increasing difficulties with completing activities of daily living including ambulation and medication compliance. Physical examination yielded no focal neurologic deficits concerning for ischemic stroke. Laboratory investigations revealed acute renal injury, metabolic alkalosis, and severe hypercalcemia. CT imaging of the head revealed no acute intracranial abnormalities. During evaluation, the patient revealed that she had been taking 15 calcium carbonate (tums) tablets daily, along with vitamin-D and calcitriol, as a result of increased symptoms of gastroesophageal reflux disease. The patient received aggressive fluid and subcutaneous calcitonin in the emergency department. She was admitted to the hospital, where she continued to receive aggressive intravenous fluids. Calcium supplementation was withheld and chlorthalidone discontinued. After a thorough negative workup, the etiology of her hypercalcemia was deemed most likely secondary to milk-alkali syndrome. She was discharged home in stable condition on hospital day 6 without receiving hemodialysis.

Conclusions:

Emergency physicians should be vigilant of MAS given the potential for high morbidity if left undiagnosed. Emergency clinicians should ask about calcium supplements, as these often won't be listed on the patient's medication list and can be purchased over the counter.

Background

Hypercalcemic crises as a result of milk-alkali syndrome is an uncommon cause of altered mental status and acute renal failure in the emergency department. Though it is uncommonly reported in the emergency medicine literature, emergency medicine clinicians should be aware of this syndrome due to significant morbidity and mortality if left undiagnosed. The diagnosis consists of a classic triad of hypercalcemia, renal failure, and metabolic alkalosis in whom other causes of hypercalcemia have been excluded (1). While the most common clinical presentation of MAS is an asymptomatic patient who is incidentally...
found to have this triad, emergency medicine clinicians should suspect MAS in patients who present with nausea, vomiting, weakness, anorexia, vertigo, and mental changes in the case of acute symptomatic hypercalcemia or who present with polyuria, polydipsia, muscle aches, psychosis, pruritis, and abnormal calcifications in cases of chronic symptomatic hypercalcemia (2). Treatment of symptomatic MAS involves withdrawal of the offending agent, immediate fluid resuscitation, and consideration of calcitonin administration (3).

**Case Presentation**

A 63-year-old woman with history of familial hypoparathyroidism, previous left cerebellar infarct, primary hypothyroidism, status post Roux-en-Y gastric bypass surgery presented to our emergency department with worsening confusion, slurred speech, generalized weakness, and failure to thrive over the course of one month. Family reported increasing difficulties with completing activities of daily living including ambulation and medication compliance. She reported no focal motor or sensory deficits but had difficulty with ambulation and was unable to self-transfer from her wheelchair to the bed. Review of systems was positive for tachypnea, polydipsia, diffuse musculoskeletal pain, dehydration, poor oral intake, nausea with nonbilious nonbloody emesis, and severe fatigue. She did not have recent head trauma, fever, chills, weight or appetite changes, abdominal pain, or respiratory symptoms. Medications included calcium citrate, vitamin D, calcitriol, chlorthalidone, and calcium carbonate (tums).

On examination, the patient was afebrile with a blood pressure of 136/74 mm Hg, heart rate of 83 beats/min, respiratory rate of 19 breaths/min, oxygen saturation of 98% while breathing room air. She was alert and oriented to person and place but not time and had difficulty following simple commands. Cranial nerves II through XII were intact. Results of motor examinations were symmetric but demonstrated 4/5 weakness in the lower extremities. Results of sensory examinations were within normal limits. Her coordination was not impaired with no dysmetria on finger-to-nose testing or heel-knee-shin testing, no nystagmus, and no dysarthria. Reflexes were symmetric. Lymph node, thyroid, cardiac, respiratory, gastrointestinal, musculoskeletal, and skin examinations identified no abnormalities. During evaluation, the patient revealed that she had been taking 5 Tums tablets in the morning, at noon, and in the afternoon (15 tablets daily), along with vitamin-D and calcitriol, as a result of increased symptoms of gastroesophageal reflux disease.

Laboratory investigations revealed a serum urea level of 57 mmol/L and serum creatinine level of 5.16 mg/dL (compared to a previous value six months prior of 1.35). Total serum calcium was found to be significantly elevated to over 16 mg per mg/dL with an ionized calcium of 7.92 mg/dL. Venous blood gas revealed an elevated pH of 7.62, low CO2 of 31 mmHg, elevated bicarbonate level of 29 mmol/L, and lactate of 2.82 mmol/L. The CBC count and markers of hepatic function were grossly normal. CT scan of the head without IV contrast demonstrated stable basal ganglia, thalamic, cortical and cerebellar calcification consistent with hypoparathyroidism without evidence of acute intracranial abnormality or hemorrhage. The diagnostic workup for the patient's hypercalcemia showed an appropriately suppressed
parathyroid hormone (PTH) response (decreased at 8.8 pg/ml) suggestive of PTH independent hypercalcemia.

In the emergency department the patient received aggressive fluid resuscitation with a 2L 0.9% normal saline bolus followed by 4 units/kg subcutaneous calcitonin. She was admitted to the hospital, where she continued to receive aggressive intravenous fluids with maintenance fluids delivered at 300 cc 0.9% normal saline per hour without experiencing volume overload. Endocrinology was consulted and recommended holding calcium supplementation until calcium normalized in agreement with Nephrology. Chlorthalidone was discontinued. She was discharged home in stable condition on hospital day 6 without receiving hemodialysis.

After a thorough negative workup, the etiology of her hypercalcemia was deemed most likely secondary to the ingestion of calcium carbonate (tums) and over supplementation of calcium, with a diagnosis of presumed milk-alkali syndrome. Her acute kidney injury was deemed most likely secondary to acute tubular necrosis (ATN), as a result of hypercalcemia leading to renal vasoconstriction, decreased water absorption, and direct injury to the renal tubules.

**Discussion and Conclusions**

Milk-alkali syndrome (MAS) resulting in hypercalcemic crisis represents a life-threatening medical emergency in the setting of excessive calcium and absorbable alkali ingestion (1, 2). MAS was first described in the early 1900s after combined milk and alkali regimens were popularized for treatment of peptic ulcer disease (2–4). After the advent of proton-pump inhibitors and H2-histamine–receptor blockade, MAS ostensibly disappeared from clinical relevance. However, current trends in calcium and vitamin D supplementation for the treatment of osteoporosis, calcium carbonate therapy for the reduction of secondary hyperparathyroidism in patients with chronic kidney disease, and widespread availability of over the counter calcium carbonate preparations (tums) has led to a resurgence of the syndrome (3, 4). In this patient, there were other factors driving hypercalcemia in addition to excessive calcium carbonate (tums) consumption. These factors included over supplementation with calcium citrate and vitamin D in addition to thiazide diuretic use leading to increased renal reabsorption of calcium. This case was unique in that it occurred in a patient with familial hypoparathyroidism.

MAS results when calcium intake exceeds renal excretion. Although controversial, the pathophysiology of MAS relates to suppression of PTH from excessive ingestion of oral calcium causing reduced conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D and intestinal resorption (2, 3). Prerenal acute kidney injury originates from hypercalcemia induced vasoconstriction and diuresis, as filtered calcium activates calcium sensing receptors in the medullary thick ascending limb of the nephron (3). Metabolic alkalosis occurs as a consequence of both ingestion of absorbable alkali and impaired renal excretion of excess bicarbonate (2, 3).

Treatment of symptomatic MAS involves withdrawal of the offending agent and immediate fluid resuscitation with intravenous isotonic saline or plasmalyte. Expert opinion remains mixed on whether
lactated ringers is suboptimal given that it contains a physiological concentration of calcium and is metabolized to bicarbonate, which may worsen metabolic alkalosis in MAS (5). To our knowledge there is currently no evidence comparing normal saline versus lactated ringer's solution in hypercalcemia or MAS (5). Affected patients are typically volume depleted as a result of hypercalcemia induced diuresis and poor oral intake in the setting of confusion. Therefore, they often require fluid resuscitation with an intravenous (IV) fluid bolus until euvoletic, followed by continuous saline infusion which serves not only to decrease total calcium concentration resulting from volume contraction but also facilitates increased renal clearance of calcium [suggested regimen of 200 to 300 mL/h titrated to a goal of achieving urine output of 100 to 150 mL/h and the patient's cardiovascular tolerance] (3, 6, 7). Loop diuretics for the treatment of hypercalcemia are no longer recommended, unless there is a high risk of fluid overload (7, 8).

In patients with symptomatic hypercalcemic crisis (calcium level greater than 14 mg/dL or severe symptoms with calcium level greater than 12 mg/dl) (7), emergency physicians should consider the administration of calcitonin to more rapidly decrease the total calcium concentration. Calcitonin is a peptide hormone that lowers calcium levels by inhibiting bone calcium resorption and increasing renal calcium excretion. It may be administered either intramuscularly (IM) or subcutaneously (SubQ) for hypercalcemia, with a commonly cited initial dose of 4 units/kg (IM or SubQ) to lower total calcium levels by up to 2 mg/dL and may be redosed every 12 hours (3, 9). In refractory cases, hemodialysis against a low- or no-calcium dialysate may be required (7). Nephrology consultation for hemodialysis should be considered in cases of total serum calcium levels above18 to 20 mg/dL with neurological symptoms, cases of refractory hypercalcemia, and patients who are unable to tolerate IV fluid hydration in the setting of heart failure or severe kidney disease (7).

Calcitonin as a sole agent is preferred over combined therapy with bisphosphonates in cases of MAS as unlike bisphosphonates (i.e., zoledronic acid, pamidronate, ect.) calcitonin is not contraindicated in cases of renal failure. Moreover, in comparison to calcitonin which has a rapid onset of action (4–6 hours) and short duration of effect (48 hours as a result of tachyphylaxis), the nadir in total calcium concentrations after IV bisphosphonate administration occurs later (typically 2–4 days) and has longer lasting effects. This is less favorable in the setting of MAS as patients may be at risk of hypocalcemia after the offending agent is discontinued (3, 7). Calcitonin may be more useful for rapidly lowering calcium in the setting of the emergency department where rapid lowering of hypercalcemia is required. In this patient, bisphosphonates were not recommended as she was deemed high risk by our endocrinology colleagues for developing hypocalcemia as a result of her underlying genetic hypoparathyroidism. Similarly, denosumab which has limited evidence for the treatment of acute hypercalcemia was deemed absolutely contraindicated in her case (7).

Emergency physicians should be vigilant of MAS given the potential for high morbidity if left undiagnosed. One of the key points to learn from this case is that the physicians should ask about calcium supplements, as these often won't be listed on the patient's medication list and can be purchased over the counter.
List Of Abbreviations

Intravenous (IV)
Intramuscular (IM)
Milk-alkali syndrome (MAS)
Parathyroid hormone (PTH)
Subcutaneous (SubQ)

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Availability of data and materials
Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Competing interests
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Authors' contributions
RL analyzed and interpreted the patient data, participated in the care of the patient, and wrote the manuscript. BM analyzed and interpreted the patient data, participated in the care of the patient, and was a major contributor in editing of the manuscript. All authors read and approved the final manuscript.

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References


