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CASE REPORT

Calcium alkali syndrome, a resurging entity: a case report and historical overview

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ABSTRACT

Background: Calcium-alkali syndrome (CAS), previously termed milk-alkali syndrome, is characterized by hypercalcemia, metabolic alkalosis, and acute kidney injury due to excessive intake of calcium and absorbable alkali. Initially associated with the Sippy diet for peptic ulcer treatment, its prevalence declined with modern gastrointestinal therapies but has resurged due to widespread calcium carbonate supplementation. Early recognition of CAS is essential to prevent hypercalcemic crises and renal dysfunction.

Case Presentation: A 60-year-old male with a history of hypertension and type 2 diabetes mellitus presented with palpitations, generalized weakness, muscle aches, polyuria, nausea, and a single episode of non-bloody vomiting. Examination revealed tachycardia (117 beats per minute) and severe hypertension (193/126 mmHg). Electrocardiography showed sinus tachycardia with premature ventricular complexes. Laboratory findings included severe hypercalcemia (18.9 mg/dL), acute kidney injury (creatinine rise from 0.8 to 2.9 mg/dL), and elevated BUN, bilirubin, total protein, white blood cell count, and CRP. Imaging ruled out alternative causes, and suppressed parathyroid hormone levels excluded hyperparathyroidism. A detailed history revealed chronic ingestion of 3–6 calcium carbonate (TUMS) tablets daily for acid reflux. Management included intravenous hydration, zoledronic acid, furosemide, and antihypertensives, resulting in calcium normalization and renal function recovery.

Conclusion: This case highlights the resurgence of CAS due to excessive over-the-counter calcium use. Early diagnosis and management, including cessation of calcium supplements, aggressive hydration, and electrolyte monitoring, are crucial in preventing complications. Long-term follow-up is essential to ensure renal function recovery and prevent recurrence.

Keywords: Calcium-alkali syndrome (Non-MeSH); Milk-alkali syndrome (Non-MeSH); Hypercalcemia (MeSH); Alkalosis (MeSH); Acute Kidney Injury (MeSH); Calcium Carbonate (MeSH).

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INTRODUCTION

The milk-alkali syndrome is characterized by the clinical triad of hypercalcemia, metabolic alkalosis, and acute kidney injury, resulting from excessive intake of calcium and absorbable alkali. The term "milk-alkali syndrome" has been updated to "calcium-alkali syndrome" (CAS) to more accurately reflect the etiology of the condition.[1] Initially associated with the consumption of large quantities of milk and absorbable alkalis, the condition was widely documented following the popularization of the Sippy diet in the early 20th century for peptic ulcer disease management.[2] Despite a decline in incidence with the advent of modern gastrointestinal therapies, CAS has seen a resurgence, attributed primarily to the excessive intake of calcium carbonate supplements. This syndrome, once considered a historical footnote, has re-emerged as a notable cause of hypercalcemic emergencies in the contemporary era, reflecting changes in dietary and medicinal practices. The renaissance of CAS highlights the intricate balance between calcium homeostasis and renal function and underscores the importance of recognizing the potential adverse effects of over-the-counter supplements on patient health.[3-5]

CASE REPORT

A 60-year-old male with essential hypertension and type 2 Diabetes Mellitus, was admitted with palpitations and generalized body weakness. The patient's symptoms started two days before the admission, he reported muscle aches and increasing fatigue, polyuria, nausea and a single episode of non-bloody, non-bilious vomiting on the morning of admission. These symptoms, coupled with palpitations, prompted him to seek medical attention. The patient had a tachycardia of 117 beats per minute and blood pressure elevated at 193/126 mmHg on presentation. An electrocardiogram (ECG) showed sinus tachycardia with premature ventricular contractions (Figure 1).

Initial laboratory workup revealed acute kidney injury (AKI), with a creatinine level of 2.0 mg/dL (0.5–1.5 mg/dL), elevated from a baseline of 0.8 mg/dL, and an increased BUN level of 27 mg/dL (7–25 mg/dL), compared to a prior value of 18 mg/dL. A comprehensive metabolic panel indicated severe hypercalcemia, with a calcium level of 18.9 mg/dL (8.6–10.3 mg/dL). Additional findings included mildly elevated bilirubin at 1.6 mg/dL (0.3–1.0 mg/dL), total protein at 9 g/dL (6.3–8.2 g/dL), white blood cell count of 18 k/uL (4.5–10.5 k/uL), and an increased C-reactive protein (CRP) level of 2.3 mg/dL (normal: ≤0.9 mg/dL).

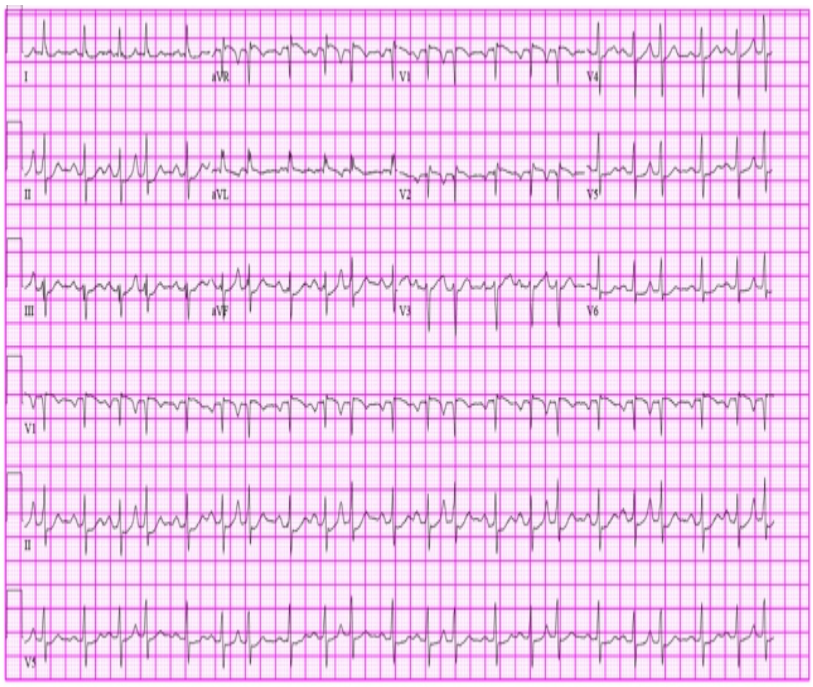

Figure 1: Electrocardiogram (EKG): Heart rate 131 beats per minute, premature ventricular complexes and a QTc interval of 440 ms

A contrast-enhanced computed tomography (CT) scan of the abdomen and pelvis ruled out bowel obstruction, abscess, or significant masses but suggested possible pyelonephritis versus chronic changes, along with findings of sigmoid diverticulosis and diffuse hepatic steatosis. A CT chest with a pulmonary embolism (PE) protocol excluded PE.

The patient received intravenous diltiazem (10 mg), metoprolol tartrate (5 mg), and labetalol (20 mg) without significant blood pressure improvement, necessitating a labetalol infusion. Given the severity of hypercalcemia, urgent treatment with IV zoledronic acid and a 2-liter saline bolus was administered, followed by IV furosemide (80 mg) to enhance calcium excretion. Continuous IV hydration with normal saline was initiated following the initial fluid resuscitation.

The patient's renal function initially worsened, with creatinine peaking at 2.9 mg/dL, requiring close monitoring while hydration therapy continued. Parathyroid hormone (PTH) levels were low at 7.8 pg/mL (11.0–75.0 pg/mL), effectively ruling out hyperparathyroidism as the cause of hypercalcemia.

Further laboratory investigations were conducted to identify non-PTH-dependent causes of hypercalcemia, including assessments of vitamin D, PTH-related peptide, light chains, serum protein electrophoresis (SPEP), 24-hour microalbumin, and angiotensin-converting enzyme (ACE) levels. Most results were within normal limits, except for slightly low vitamin D (19.3 ng/mL; deficiency <20 ng/mL) and ACE levels (<5 U/L; 16–85 U/L). A review of prior medical records indicated a mild hypercalcemia episode (10.4 mg/dL) four months earlier. Further inquiry revealed the patient had been consuming 3–6 tablets of TUMS daily for several weeks to manage acid reflux. This confirmed a diagnosis of CAS due to excessive calcium-containing antacid use, prompting the immediate discontinuation of calcium supplements and continued hydration therapy.

Renal function improved with ongoing hydration, as creatinine levels decreased to 1.2 mg/dL, with a glomerular filtration rate exceeding 60 mL/min. Calcium levels normalized, and blood pressure stabilized, allowing a transition from IV labetalol infusion to an oral regimen of amlodipine, metoprolol tartrate, and hydralazine.

Upon discharge, the patient was advised to maintain adequate hydration, monitor blood pressure daily, and avoid nonsteroidal anti-inflammatory drugs (NSAIDs) and calcium supplements. A structured outpatient follow-up was arranged for continued monitoring and treatment adjustments, including management of essential hypertension and regular evaluation of calcium and electrolyte levels.

DISCUSSION

The adverse effects of milk and alkali consumption were first noted by Hippocrates over two thousand years ago. In 1915, Bertram Sippy introduced a dietary regimen for peptic ulcer disease, involving hourly milk and cream consumption, gradually adding eggs and cereal over ten days, supplemented with alkaline powders containing magnesium, sodium bicarbonate, and bismuth sub-carbonate. Designed to neutralize gastric acidity, the regimen also included periodic gastric aspiration for at least four weeks during inpatient care. The historical evolution of treatment strategies highlights the impact of dietary and medicinal practices on the emergence of CAS in medical discourse.[2]

Sippy's treatment gained popularity, but some patients treated with high doses of calcium and sodium bicarbonate developed symptoms such as headache, nausea, vomiting, dizziness, anorexia, musculoskeletal pain, weakness, mental clouding, and renal failure.[6,7] Subsequent investigations identified a chronic form of toxicity associated with the regimen. In 1936, Cope reported significant hypercalcemia, alkalosis, and renal failure in patients undergoing peptic ulcer treatment, with rapid normalization upon cessation of therapy.[8] In 1949, Burnett CH, et al., described a syndrome in six individuals consuming milk and absorbable alkali for 2 to 30 years, characterized by

alkalosis, hypercalcemia, metastatic calcification, and irreversible renal failure.[9] This differed from Cope's findings, where renal insufficiency was reversible upon discontinuation of treatment.

Hardt and Rivers' accounts were considered early-phase manifestations of CAS, Cope's findings represented an intermediate stage, and Burnett's descriptions depicted a terminal, irreversible phase. In 1963, Punsar classified CAS into "reversible" and "irreversible" subtypes, aligning with Cope's and Burnett's observations, respectively, with the latter characterized by metastatic soft tissue calcification.[10] During the 1950s and 1960s, CAS was frequently diagnosed, with review articles outlining its clinical patterns.[11,12] The prevalence declined following the introduction of nonabsorbable antacids and later histamine-2 (H_2) receptor antagonists.[13] By 1975, Jamieson reported that CAS accounted for less than 1% of hypercalcemia cases, reflecting its reduced occurrence with advancing peptic ulcer treatments.[14]

During the 1970s and early 1980s, CAS became infrequent, with a shift in its clinical presentation. It primarily emerged in patients consuming lower doses of calcium (5–10 g daily), mainly in the form of calcium carbonate, an alkaline compound providing both calcium and alkali.[15] Predisposing factors included vomiting, hypokalemia, hypertension, chronic renal insufficiency, hemorrhage, and hydrochlorothiazide therapy. Notably, serum phosphate levels were consistently lower than in historical cases, suggesting a transition in CAS etiology from dairy-rich diets to excessive calcium carbonate supplement use.[3]

An analysis of 54 patients from 1983 to 2004 identified calcium carbonate as the primary source of calcium and absorbable alkali. Only 19 patients had significant dairy consumption, and just 11 exhibited elevated serum phosphorus levels. Surgical exploration of the parathyroid gland was conducted in three cases, while 20 patients suffered irreversible renal impairment, highlighting a diagnostic oversight in recognizing CAS.[4] In a study from 1992 to 1995 at a university-affiliated hospital, 16% of patients admitted for hypercalcemic emergencies were diagnosed with CAS, surpassing cases linked to multiple myeloma.[5] All had consumed calcium carbonate, often through multiple over-the-counter supplements, suggesting a higher prevalence of CAS than previously acknowledged. The increased incidence is largely attributed to widespread calcium supplementation, particularly among postmenopausal women managing osteopenia/osteoporosis. Calcium carbonate is also frequently used in chronic kidney disease to control secondary hyperparathyroidism and remains a common over-the-counter antacid. A single-center hospital cohort study identified CAS as the third leading cause of hypercalcemia-related hospital admissions, following hypercalcemia of malignancy and primary hyperparathyroidism. Notably, it was the second most common cause of severe hypercalcemia, accounting for 8.8% of cases, underscoring its growing clinical significance.[16] This aligns with our case, where the patient developed severe hypercalcemia after excessive over-the-counter TUMS consumption.

The pathogenesis of calcium-alkali syndrome (CAS) is complex and involves two stages: the generation and maintenance of hypercalcemia.[17] Hypercalcemia induces renal vasoconstriction, reducing the glomerular filtration rate (GFR), and activates calcium-sensing receptors in the medullary thick ascending limb, inhibiting the Na-K-2Cl cotransporter. This leads to natriuresis, impaired antidiuretic hormone (ADH) response, and volume depletion, which enhances bicarbonate reabsorption, contributing to metabolic alkalosis. The combination of increased alkali intake, reduced GFR, and alkalosis sustains hypercalcemia. Factors like vomiting and diuretics further exacerbate the condition. Severe hypercalcemia can trigger an acute presentation, while chronic mild hypercalcemia with alkalosis predisposes individuals to nephrocalcinosis and chronic kidney disease.[1,15,17]

Hydrochlorothiazide use increases CAS risk by enhancing renal calcium reabsorption and promoting contraction alkalosis via volume depletion.[18] Reduced GFR due to chronic kidney disease, angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, or vitamin D supplementation also amplifies susceptibility. Excessive calcium intake downregulates calcitriol to maintain homeostasis, but passive calcium absorption continues, leading to hypercalcemia.[19] Unlike historical cases linked to milk consumption, modern CAS cases often present with hypophosphatemia due to the phosphate-binding nature of calcium carbonate. Hypomagnesemia is also common, likely due to hypercalcemia impairing renal magnesium reabsorption.[16] Low intact parathyroid hormone (PTH) levels help differentiate CAS from primary hyperparathyroidism.[15,16]

Many CAS cases are asymptomatic, with hypercalcemia, alkalosis, and renal dysfunction often detected incidentally. Symptomatic cases may present with dehydration, nausea, vomiting, constipation, and altered mental status. Serum calcium levels of 12–15 mg/dL can cause reversible GFR reduction through renal vasoconstriction and volume contraction.[19] Management involves discontinuing calcium intake and ensuring adequate hydration. Furosemide may aid calcium excretion, while severe hypercalcemia may require bisphosphonates like pamidronate.[1,20] However, bisphosphonates can induce hypocalcemia, as observed in a case series where six of eleven CAS patients developed this complication.[16] Nephrology consultation is advisable, particularly in cases of severe hypercalcemia or irreversible renal damage.

Our case demonstrates extreme

hypercalcemia in an elderly patient due to excessive calcium supplement intake, reinforcing the diagnosis of CAS. Historically, many cases have been linked to calcium carbonate-containing antacids.[1] Given that CAS is a diagnosis of exclusion, thorough history-taking and physical examination are essential. In contemporary clinical practice, assessing over-the-counter medication use is crucial, as many products contain calcium.

CONCLUSION

Calcium-Alkali Syndrome represents a fascinating case study in the evolution of disease, from its origins tied to dietary remedies to its modern incarnation driven by supplement overuse. Despite its changing etiology, the core principles of CAS management remain centered on the cessation of calcium supplementation and the correction of fluid and electrolyte imbalances. The enduring relevance of CAS, from Hippocrates to the present day, illustrates the complex interplay between nutrition, medication, and renal physiology, offering enduring insights into the prevention and treatment of hypercalcemia and metabolic disturbances. This historical progression, from diet-induced pathology to supplement-associated complications, underscores the importance of continued education and awareness among healthcare providers and patients regarding the potential risks of excessive calcium intake.

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AUTHORS' CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

YA & DC: Identification and diagnosis of the case, drafting the manuscript, critical review, approval of the final version to be published

UM: Management of the case, drafting the manuscript, critical review, approval of the final version to be published

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Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST

Authors declared no conflict of interest, whether financial or otherwise, that could influence the integrity, objectivity, or validity of their research work.

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DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request

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