CASE REPORT

Milk-Alkali Syndrome: A Century-old Cause of Hypercalcemia Requires the Addition of Venous Blood Gas in Hypercalcemia Workup

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Abstract

The Milk-Alkali syndrome (MAS) is identified by the triad of high serum levels of calcium, metabolic alkalosis, and acute kidney injury, usually caused by consuming excessive amounts of calcium and absorbable alkali. If not treated promptly, the syndrome can result in rapid hypercalcemia, acute renal failure, and metastatic calcification. Notably, an increasing number of cases of MAS have been observed, potentially due to the rampant use of calcium-based over-the-counter supplements for the prevention and treatment of osteoporosis in postmenopausal women. Herein, we report a case of severe hypercalcemia due to prolonged intake of calcium carbonate supplements in the absence of any alkali. The case report highlights the importance of including venous blood gas (VBG) analysis as a part of the workup for hypercalcemia, as metabolic alkalosis can help clinch the diagnosis of MAS in the setting of severe hypercalcemia.

Introduction

The Milk-Alkali syndrome (MAS) consists of the triad of hypercalcemia, metabolic alkalosis, and various degrees of renal failure associated with the ingestion of large amounts of calcium and absorbable alkali. This syndrome was discovered in the 1930s after treatment of peptic ulcer disease with milk and sodium bicarbonate had become common.1 Once a classic cause of hypercalcemia, the MAS virtually disappeared with the advent of new therapies for peptic ulcer disease and, by 1985, was considered the cause of <1% of cases of hypercalcemia.2

In recent times, there has been a notable rise in the occurrence of MAS. This surge can be attributed to the widespread usage of over-the-counter calcium preparations among postmenopausal women as a means of preventing and treating osteoporosis. Moreover, healthcare professionals often prescribe calcium carbonate to individuals with chronic kidney disease to prevent the development of secondary hyperparathyroidism. In light of the evolving research, some experts have proposed renaming the syndrome as a calcium-alkali syndrome.3 MAS now accounts for >10% of the cases of hypercalcemia and is believed to be the third most common cause of in-hospital hypercalcemia after hyperparathyroidism and malignant neoplasms.4

Case Description

A 71-year-old normotensive, nondiabetic, and euthyroid female presented with confusion, irrelevant talks, and urinary incontinence. Her blood pressure was 160/84 mm Hg, and random blood glucose was found to be 125 mg/dL. Routine blood investigations revealed hemoglobin: 13.2 g/dL (normal range: 12.0–15.0), blood urea: 103 mg/dL (normal range: 20–40), serum creatinine: 4.2 mg/dL (normal range: 0.7–1.2), total calcium: 14.9 mg/dL (normal range: 8.5–10.5), phosphorous: 4.2 mg/dL (normal range: 3.5–4.5), albumin: 3.9 g/dL (normal range: 3.4–4.6), her venous blood gas (VBG) confirmed metabolic alkalosis, with a pH of 7.540, partial pressure of carbon dioxide 52 mm Hg, partial pressure of oxygen 51 mm Hg, and hydrogen carbonate 42 mmol/L. She gave a history of taking analgesics for joint pains and supplements of calcium carbonate for osteoporosis for the last 20 years.

Other investigations revealed serum angiotensin-converting enzyme of 36 U/L (normal range: 8–52), thyroid stimulating hormone of 4.2 mIU/mL (normal range: 0.5–5.0), 25-hydroxy (OH)—vitamin-D of 40.4 ng/mL (normal range: 30–100), and normal serum protein electrophoresis. Despite high serum calcium level, her parathyroid hormone (PTH) was not suppressed, and her intact PTH level was found to be 46.1 pg/mL. Technetium Septambib scan did not localize any parathyroid adenoma, and the positron emission tomographic scan ruled out the possibility of any paraneoplastic syndrome. On the basis of metabolic alkalosis, even in the setting of severe renal dysfunction, and excluding other causes of hypercalcemia, MAS was diagnosed. On further questioning, the patient admitted to perhaps taking more calcium than she should have. But there was no history of any antacid intake.

She was treated with saline diuresis and an injection of calcitonin 200 units, given subcutaneously thrice daily for 2 days, and her symptoms and renal functions started improving. Within 1 week after admission, her renal functions improved significantly, her blood urea: 50 mg/dL, serum creatinine: 1.7 mg/dL, and her total calcium came down to 8.5 mg/dL, and she was discharged with clear instructions to avoid any calcium carbonate supplements.

Discussion

Despite considerable clinical experience, there is a lack of substantial data regarding the underlying causes of MAS. Over the years, various factors have been suggested as potential contributors, such as gastric juice depletion, preexisting renal disease, inadequate chloride intake, hemorrhage, anemia, and impaired liver function. However, the precise pathogenesis remains poorly understood. To diagnose MAS, it is essential to observe the ingestion of excessive amounts of both calcium and absorbable alkali. What constitutes “excessive” is unclear but generally indicates at least 4–5 gm of calcium carbonate daily.5

The development of hypercalcemia requires not only excessive calcium intake but also the inability to effectively excrete the excess calcium. This is because the skeletal system has a limited capacity to buffer calcium. To maintain appropriate serum calcium levels, precise regulation of calcium absorption from the small intestine and excretion by the kidneys is crucial.

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Furthermore, individual variations in the buffering capacity of bone may influence an individual’s susceptibility to developing hypercalcemia. When calcium intake increases, it results in a reduction in the kidneys’ ability to convert vitamin D into its active form, known as 25-hydroxylation. Consequently, there is a significant decrease in the fractional absorption of calcium in the small intestine. In certain individuals, despite ongoing calcium ingestion and suppressed levels of 1,25-OH vitamin D, there is persistent high urinary calcium excretion, indicating elevated intestinal absorption. Under normal circumstances, renal calcium excretion closely reflects calcium absorption. However, if substantial amounts of calcium are consistently ingested, and the kidneys are unable to excrete it effectively, hypercalcemia becomes a foreseeable outcome. In some cases, the failure to adequately suppress calcitriol levels may contribute to the development of MAS in individuals with high oral calcium intake.

The PTH level should be suppressed by the high serum calcium level in patients with MAS. But in the setting of severe renal dysfunction, the PTH level is raised. Renal dysfunction is also associated with metabolic acidosis. But in the setting of MAS, metabolic alkalosis is the essential feature. Differentiating MAS from other causes of hypercalcemia is important as treatment is supportive. Adequate hydration to correct hypovolemia, along with loop diuretics, like furosemide, to increase urinary calcium excretion, may be sufficient to correct hypercalcemia. Patients diagnosed with MAS should generally avoid the use of bisphosphonates due to their potential to induce prolonged hypocalcemia.

**Conclusion**

The recent resurgence of MAS can be attributed to the increased awareness of osteoporosis and the widespread use of calcium carbonate supplements for preventive purposes. It is crucial to educate the public about the potential adverse effects of exceeding the recommended dosage of calcium supplementation. It is generally considered safe to have a daily intake of elemental calcium of no >2 gm. However, even doses lower than 2 gm per day may lead to MAS if other predisposing factors are present.

The exact mechanism of how MAS develops is still not fully understood. However, there appears to be a unique interplay between hypercalcemia and alkalosis within the kidneys. This interplay creates a self-reinforcing cycle, contributing to the clinical manifestation of MAS. VBG analysis should be included in the workup of hypercalcemia as the presence of metabolic alkalosis can help clinch the diagnosis of MAS.

In general, MAS has a good prognosis when it is appropriately diagnosed and treated. Timely and effective management plays a crucial role in improving outcomes for individuals with MAS. Treatment typically involves addressing the underlying causes, discontinuing excessive calcium and alkali intake, restoring fluid and electrolyte balance, and managing any associated complications.

If adequately managed, even complicated MAS cases associated with posterior reversible encephalopathy syndrome may also have a favourable outcome. The general public, as well as healthcare professionals, should be aware of the potential negative consequences of consuming excessive quantities of calcium carbonate.

**Learning Points**

- Healthcare providers and the general public, at large, need to be educated about calcium supplementation and their potential negative effects if the recommended dosage is exceeded.
- Metabolic alkalosis in the setting of hypercalcemia-induced acute kidney injury should alert the physician about MAS, the third most common cause of hypercalcemia in hospitalized patients.
- Venous blood gas (VBG) analysis is a simple and inexpensive test that should be included as part of the workup for hypercalcemia, as metabolic alkalosis can help clinch the diagnosis of MAS before moving to expensive nuclear imaging studies.

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