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Case Report

Milk-alkali syndrome in a rare environment associated with an uncommon feature

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ABSTRACT

Milk-alkali syndrome is a rare syndrome noted in the premodern era during treatment of peptic ulcer disease with calcium-enriched milk and absorbable alkali. It was associated with hypercalcemia, alkalosis, renal insufficiency and hyperphosphatemia during that era. Its incidence fell following the advent of modern era forms of peptic ulcer treatment. However, the syndrome is re-emerging owing to the availability of over-the-counter calcium carbonate-containing antacids in this modern era but with a low incidence of hyperphosphatemia. The syndrome is rare in our environment and has not been reported. Here, we report a rare case of milk-alkali syndrome associated with hyperphosphatemia in an adult male who presented to us after weeks of ingestion of antacids. He was managed accordingly and made full recovery after four weeks.

Keywords: Antacids, Alkalosis, Hypercalcemia, Hyperphosphatemia, Milk-Alkali Syndrome, Nigeria

INTRODUCTION

Milk-Alkali Syndrome is a term that was coined more than a 100years ago to characterize the pathophysiologic events that preceded the excessive ingestion of antacids containing a high amount of calcium-enriched milk and absorbable alkali during the treatment of peptic ulcer- the so-called Sippy regimen. The modern era uses of histamine-2 receptor blockers and proton pump inhibitors in peptic ulcer treatment have reduced the occurrence of this syndrome since the 1970s. However, recent reports have suggested the re-emergence of this syndrome due to easy access to the over-the-counter calcium carbonate and alkali (usually sodium bicarbonate) containing antacids and are now been regarded as one of the commonest causes of hypercalcemia. The syndrome is characterized by hypercalcemia, metabolic alkalosis with some level of renal impairment but rarely with hyperphosphatemia in the modern era. Here, we report a rare case of Milk-Alkali syndrome associated with hyperphosphatemia.

CASE REPORT

Our case is of a 66-year-old retired male police officer presented to us in the metabolic clinic of the University of Port Harcourt Teaching Hospital with three weeks history of frequency of urination, nocturia, and polydipsia which have been worsening progressively over the course of the three weeks prior to presentation. He voids urine more than 10 times a day, five to seven times at night and drinks about four liters of water in 24hours. He had presented to a private hospital based on the aforementioned symptoms a week before where he was investigated for diabetes mellitus, urinary tract infection and prostatic diseases but with negative result hence his presentation to our hospital. His medical history had been uneventful until about three weeks prior to the onset of

his present symptoms when he started experiencing recurrent bouts of very distressing dyspepsia. The dyspepsia, which is temporarily relieved by ingesting this antacid (Gaviscon peppermint liquid from Reckitt Benckiser Nigeria LTD), made him totally dependent on this medication for the past six weeks and he had continued to self-medicate with this antacid while his non-dyspeptic symptoms (frequency of urination, nocturia, and polydipsia) continued. On further questioning, he reported being ingesting an estimated 40 to 60 milliliters (ml) in divided doses per day. This brand of antacids contains 133.3mg of sodium bicarbonate per 5 ml and 80mg of calcium carbonate per 5ml. On examination, he appears healthy looking and in no acute distress, afebrile, anicteric, mildly pale, not dehydrated and with no signs of peripheral edema. His weight was 79kg with a height of 1.72m hence mildly overweight (BMI 25.3kg/m2). He was normotensive (130/80mmHg) with a peripheral pulse of 89 beats per minute and respiratory rate of 18 breath cycles per minute. He was well orientated in time, person and place with no signs of altered sensorium nor neurologic deficits. He had normal breath sounds and a normal heart beat on auscultation. His abdomen was full, moves symmetrically with respiration with moderate epigastric tenderness but no mass or organ enlargement was felt on abdominal palpation. Digital rectal examination of the prostate done found no abnormality including examination of the eye, nose and the throat.

The investigations ordered with their results are displayed on Table 1 confirming hypercalcemia (plasma albumin-corrected total calcium of 3.06mmol/l; normal 2.1-2.6, corrected using the formula: plasma measured calcium + (40-plasma albumin in g/l) x 0.02)) , metabolic acidosis (plasma bicarbonate of 38mmol/l; normal 24-30), renal insufficiency (plasma urea of 11.8mmo/l; normal 2.4-6.0) and (creatinine of 220µmol/l; normal 60-120) and hyperphosphatemia (plasma inorganic phosphate of 1.9mmol/l; normal 0.9-1.5).

Table 1: Laboratory investigation results and their reference ranges.

Investigations	Values	Reference range
First set		
Plasma fasting blood glucose	4.1	3.5-5.5 mmol/l
Plasma sodium	140	127-142 mmol/l
Plasma potassium	3.8	3.4-4.8 mmol/l
Plasma bicarbonate	38	24-30 mmol/l
Plasma urea	11.8	2.2-6.0 mmol/l
Plasma creatinine	220	60-120 µmol/l
Serum total PSA	1.4	0-4 ng/ml
Urine microscopy and culture	NAD	-
Second set		
Serum intact PTH	3.0	10-65 ng/ml
Total plasma calcium	3.0	2.1-2.6 mmol/l
Plasma inorganic phosphate	1.9	0.9-1.5 mmol/l
Plasma albumin	38	34-50 g/l
Albumin-corrected calcium*	3.06	2.1-2.6 mmol/l

mmol/l = millimole per liter; µmol/l = micromole per liter; g/ml = gram per liter; GFR = Glomerular filtration rate; mls/min = milliliter per minute; NAD = No Abnormality Detected; ng/ml = nanogram per milliter; PSA = prostate-specific antigen. *Corrected using the formula: plasma measured calcium + (40 – plasma albumin in g/l) x 0.02.9

Table 2: Trend of weekly descent of plasma albumin-corrected calcium, inorganic phosphate, bicarbonate, urea and creatinine concentrations with gradual ascent of serum intact PTH.

Plasma/serum analyte	Week 1 (basal)	Week 2	Week 3	Week 4	Week 5
Calcium mmol/l	3.00	2.9	2.7	2.2	2.2
Inorganic phosphate (mmol/l)	1.9	1.8	1.6	1.3	1.2
Bicarbonate (mmol/l)	38	36	32	29	29
Urea (mmol/l)	11.8	10.4	6.9	5.3	3.8
Creatinine (µmol/l)	220	180	140	110	100
Intact PTH (ng/ml)	3.0	7.0	16	25	28

mmol/l = millimole per liter; µmol/l = micromole per liter; g/ml = gram per liter; ng/ml = nanogram per milliliter.

Considering his history, physical examination findings and laboratory investigations, no features were found suggestive of malignant disease or hyperparathyroidism. A diagnosis of milk-alkali syndrome was made with associated hypercalcemia, metabolic alkalosis, renal impairment and hyperphosphatemia. Following

confirmation of the diagnosis, the patient declined hospital admission on the ground that he was feeling better and preferred to be treated as an out-patient. Out-patient management of the patient commenced immediately with stoppage of the antacids, adequate hydration with oral fluids, reduction of high calcium and phosphate diet, avoidance of prolonged inactivity and was placed on oral omeprazole 20mg twice daily for his dyspepsia. Since he was unusually well hydrated, a low-dose oral furosemide 20mg daily was also commenced.

He was monitored during the course of his treatment with weekly plasm albumin-corrected calcium, phosphate, urea, creatinine, and serum intact PTH laboratory investigations. By the fourth week, all symptoms, vital signs and laboratory parameters of the patient had all normalized as shown in Table 2. By the fifth week as shown in Table 2 also, confirmatory investigations were carried out and all results revealed complete resolution of hypercalcemia, metabolic acidosis, hyperphosphatemia and restoration of normal renal functions. Finally, all medications (furosemide and omeprazole) following full recovery were stopped and the patient was counseled adequately against self-medication.

DISCUSSION

Milk-alkali syndrome is caused by the ingestion of large quantities of calcium-enriched milk and absorbable alkali resulting in hypercalcemia, metabolic alkalosis and some degree of renal deterioration.[1] The syndrome was first observed in the twentieth century during the premodern era treatment of peptic ulcer with so-called Sippy regimen (Calcium-enriched milk and alkali) which was the standard treatment for the disease at that time.[2] Consequently, the treated patients developed the characteristic features of the syndrome. The premodern era Milk-Alkali syndrome was also associated with hyperphosphatemia due to large quantities of phosphate-enriched milk used for the treatment of peptic ulcer. The norm in the modern era is usually low or low-normal phosphate levels reflecting low consumption of milk and the phosphate-binding properties of calcium carbonate.[3]

The hyperphosphatemia finding in our patient is at variance with the norm of the modern era Milk-alkali syndrome. Despite the introduction of histamine-2 receptor antagonist and proton pump inhibitors in the treatment of symptoms of peptic ulcer disease, the syndrome is still being reported due to consumption of over-the-counter calcium-containing antacid.[4] The syndrome is now the third most common etiologic factor for hypercalcemia after hyperparathyroidism and malignancy.[4] The syndrome has also been reported among those on calcium carbonate for various conditions including osteoporosis.[5]

The syndrome could present acutely (with nausea, vomiting, dizziness, and irritability) sub-acutely or chronically (with polyuria, nocturia, polydipsia, metastatic calcifications).[6] The hypercalcemia and alkalosis associated with this syndrome are central to all the biochemical derangements and clinical features of the syndrome.[7] In the hypercalcemia state, elevated calcium triggers renal vascular constriction and thereby depressing glomerular filtration rate.[3,4,8]

Calcification of tubular cells inhibits the tubular response to antidiuretic hormone thereby increasing sodium and water excretion, which presents clinically as frequency of urination, nocturia, and polydipsia as observed in this patient.[9] The polydipsia being due to contraction of extracellular fluid volume and reduction of plasma osmolality induced by increased urinary water and sodium excretion. Dehydration, which is a cardinal feature of the syndrome as reported previously was not noticed in our patient, probably due to his polydipsic status.[7,10]

Hypercalcemia also depresses parathyroid hormone secretion via negative feedback mechanism which in turn reduces the renal excretion of phosphate and bicarbonate with resultant hyperphosphatemia and alkalosis.[4,6] The Alkalosis due to PTH depression, including that due to excess calcium carbonate and bicarbonate consumption increase renal reabsorption of calcium further, aggravating the hypercalcemia.[4,6] A vicious cycle ensues as the consumption of the causative agent continues.

Diagnosis of the syndrome requires a high index of suspicion coupled with a detailed history of ingestion of its precursor agents and observation of its core features of hypercalcemia, metabolic alkalosis and some level of renal impairment among other biochemical features and exclusion of its differentials.

Treatment involves discontinuation of the causative agent in this case antacids, optimal hydration, furosemide after adequate rehydration, use of bisphosphonates to inhibit calcium mobilization from bone and dialysis in life-threatening cases.[10] Patients make full recovery in most cases as in the index case.

CONCLUSION

In conclusion, Milk-Alkali syndrome can present challenges to the medical practitioners if adequate history and a high index of suspicion, which were the key we had to make the diagnosis and successfully treat this patient, are not put into play in its management.

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