

Hypercalcemia and Upper GI Symptoms

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We present here a 78-year-old gentleman who lived alone in an apartment. He was diagnosed with moderate Alzheimer's dementia and although he was physically independent, he required his friend's support in cognitive tasks such as managing his finances. He was brought to the Emergency Department by his friend because of three days of generalized weakness and decreased appetite. He was having difficulty articulating his thoughts and the friend felt him to be more confused than usual. The patient was also known for type 2 diabetes, hypertension and dyslipidemia. His medications included acarbose, atorvastatin, donepezil, metformin, pioglitazone, and ramipril. At the time of presentation, the patient was unable to answer questions appropriately however, he denied any other symptoms other than weakness. According to the friend there was no history of recent medication changes, overdoses or substance use. She had noticed, however, that the patient had been constipated, was consuming more water over the past few days and was urinating more frequently.

On physical examination, all vital signs were normal and cardiopulmonary and abdominal exams were unremarkable. The patient was delirious but there were no focal neurological deficits. Laboratory investigations revealed a normal urinalysis and complete blood count. However, the extended electrolyte panel showed elevated total calcium at 3.72 mmol/L with the ionized normalized value elevated at 2.23 mmol/L (normal ranges: 2.12–2.62 mmol/L and 1.15–1.32 mmol/L respectively). Venous pH was alkalotic at 7.45. There was also evidence of kidney injury with creatinine at 200 micromol/L. The ionized calcium decreased to 1.57 mmol/L with intravenous hydration. He was admitted to our internal medicine clinical teaching unit for further work up and management.

Parathyroid hormone level was found to be in the low normal range at 2.1 pmol/L (normal range 1.5–9.3 pmol/L).

25-hydroxyvitamin D was in the normal range at 57 nmol/L (normal range 50–125 nmol/L) and 1, 25-hydroxyvitamin D was low at 6 pmol/L (normal range 90–174 pmol/L). Serum protein electrophoresis was negative for a monoclonal peak. The patient underwent computed tomography scans of his chest, abdomen, pelvis and spine to assess for suspicious nodules or lytic bone lesions. All scans were negative.

As the hypercalcemia improved, the patient's mental status improved and he could respond more clearly to questions. He indicated that he had experienced chronic indigestion without abdominal pain for the past 3–4 years for which he had been taking a large number of chewable calcium carbonate antacid tablets (TUMS). He was consuming approximately one bottle of TUMS Regular strength per week – equivalent to approximately 10 grams of calcium per day – in addition to his usual intake of yogurt and cheese. We strongly suspected that his hypercalcemia was related to this excess calcium consumption combined with some baseline kidney injury, resulting in acute on chronic injury through hypercalcemia-induced diuresis.

A key question that remained was whether this excessive self-treatment was simply an unusual behaviour in the context of his dementia or whether there was indeed a source of gastrointestinal discomfort, such as peptic ulcer disease (PUD). The patient's abdominal exam was unremarkable, but a steady decline in his hemoglobin level was noticed in hospital from 151 g/L to 112 g/L over a week, which could not be attributed to dilution from IV hydration alone. There was no evidence of overt bleeding or hemolysis and his iron profile was not suggestive of iron deficiency; however, given the acute hemoglobin drop and history of dyspepsia, the gastroenterology service was consulted. An esophagogastroduodenoscopy was performed, which showed multiple small non-bleeding ulcers in the gastric antrum and

duodenum, which were biopsied. The patient was started on pantoprazole and was advised not to take TUMS anymore.

By discharge, his ionized calcium level and creatinine had normalized and the hemoglobin was on an upward trend. The pathology result from the gastric biopsy was positive for *Helicobacter Pylori* and the patient was started on eradication treatment in the outpatient clinic.

Discussion

Dr. Bertram Welton Sippy (1866–1924) was the creator of the Sippy Regimen for treatment of acute PUD. This consisted of hourly ingestion of milk and cream products along with calcium containing antacids (“sippy powders”) to neutralize the hyperacidic gastric environment thought to be responsible for PUD.¹ This regimen, although effective in the short term, had many adverse effects including vomiting, musculoskeletal pains, extreme fatigue and kidney injury. It was in 1936 when hypercalcemia was identified as the main culprit of these adverse effects, and it was recognized as milk alkali syndrome (MAS). Hypercalcemia results in activation of calcium sensing receptors in the kidneys and inactivation of the sodium-potassium-chloride co-transporter. This leads to excretion of the excess calcium along with water and dehydration, if fluid intake is not adequate. This volume contraction along with the excess base (carbonate from the calcium carbonate ingested) can lead to metabolic alkalosis. Dehydration, calcium-mediated renal vasoconstriction, acute tubular necrosis, renal parenchymal calcifications, and nephrolithiasis all contribute to acute and chronic renal failure in the context of hypercalcemia.

Since the introduction of histamine-2 receptor blockers and proton pump inhibitors for PUD, MAS had become a rare entity, accounting for <1% of cases of hypercalcemia. However, we are experiencing a resurgence of this since the 1990s.^{2,3} In contrast to traditional MAS, which was mainly seen in young men with PUD, the population at risk has more recently changed. The rising prevalence of osteoporosis resulting from an expanding post-menopausal population and more glucocorticoid-treated patients (e.g., with autoimmune diseases, organ transplant) has led to increased calcium and Vitamin D use for osteoporosis prevention and treatment, resulting in the re-emergence of MAS.^{4,5}

While hypercalcemia in this case was due to overconsumption of TUMS for PUD symptoms, hypercalcemia itself has also been implicated in the propagation of PUD by inducing gastrin and gastric acid hypersecretion. Many studies since the 1970s demonstrated that hypercalcemia induced by oral or intravenous administration of calcium significantly increased serum gastrin levels as well as basal gastric acid secretion in normal patients. A small double-blinded randomized controlled study in 2009 by Ceglia and colleagues showed that patients randomized to

Cinacalcet for 11 days had increased serum gastrin level and gastric acid secretion when compared with placebo.² Although this trial was small, it sheds light on the role of calcium sensing receptors (CaSR) in gastric acid secretion. Cinacalcet is a calcimimetic, which activates CaSR expressed by G cells in the stomach resulting in gastrin secretion which then stimulates hydrochloric acid production by Parietal cells. This is a possible mechanism explaining the long-standing association between hypercalcemia and PUD.^{2,3} Although, our patient’s peptic ulcers were most likely due to *Helicobacter Pylori*, the possible contribution of chronic hypercalcemia from chronic TUMS ingestion towards the worsening of the PUD deserves to be mentioned. Older patients, in general, deal less well with ingested calcium than younger patients due to impaired bone metabolism and mineralization as well as reduced renal excretion owing to baseline renal impairment.⁴ This could result in a vicious cycle where the hypercalcemia worsens the PUD symptoms causing the patient to ingest more TUMS thus, worsening the hypercalcemia and PUD symptoms in turn.

In conclusion, this case report brings forth the differential diagnosis of MAS for hypercalcemia, which has been increasing in prevalence.^{4,5} It also draws attention to a link between hypercalcemia and the pathophysiology of PUD, and highlights the importance of thorough medical history taking for making the correct diagnosis. In addition, we encourage the readers to not stop their efforts at merely the diagnosis and treatment of the hypercalcemia but instead, to further investigate the trigger for MAS, such as gastrointestinal symptoms. Had the patient not undergone endoscopic investigations, the *H. Pylori* infection would have gone undiagnosed for a longer time and may have resulted in further complications.

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