47-Year-Old Woman With Dizziness, Weakness, and Confusion

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A 47-year-old woman presented to the emergency department with symptoms of weakness, dizziness, and forgetfulness of 1 week's duration. She also noted worsening somnolence, painful lower-extremity paresthesias, and persistent vaginal bleeding that had lasted more than a year. She had lost 13.6 kg (30 lbs) during the previous 6 months while taking an over-the-counter weight loss supplement containing vitamin B_6, chromium, magnesium, coenzyme Q10, and several plant extracts.[1]

The patient's medical history was notable for nicotine dependence, frequent alcohol use, long-standing low back pain, and dyspepsia. In addition to the weight loss supplement, her only other medications were ibuprofen (up to 3600 mg/d) and calcium carbonate antacid (up to 4500 mg/d). She did not have a primary care physician and had not received age-appropriate screening for more than 10 years.

The patient was an obese woman (body mass index, 30.1 kg/m^2), who appeared dehydrated on presentation but was otherwise hemodynamically stable and in no distress. Her vital signs were as follows: oral temperature, 36.6°C; supine heart rate, 99 beats/min; blood pressure, 180/92 mm Hg; respiratory rate, 18 breaths/min, and oxygen saturation, 99% while breathing room air. She was somnolent with a blunted affect, slowed speech, and bilateral lower-extremity hyperesthesia distal to the ankles. Pelvic examination showed moderate vaginal bleeding without abnormalities on the speculum, bimanual, or rectovaginal examinations. Findings on the remainder of her examination were unremarkable.

Initial laboratory analysis yielded the following results (reference ranges provided parenthetically): hemoglobin, 7.0 g/dL (12.0-15.5 g/dL); leukocyte (white blood cell) count, 7.8 × 10^9/L (3.5-10.5 × 10^9/L); platelet count, 154 × 10^9/L (150-450 × 10^9/L); prothrombin time, 12.8 s (8.3-10.8 s), and international normalized ratio, 1.3 (0.9-1.2). An electrolyte panel showed the following: sodium, 138 mEq/L (135-145 mEq/L); potassium, 4.5 mmol/L (3.6-4.8 mmol/L); chloride, 100 mmol/L (100-108 mmol/L); bicarbonate, 30 mEq/L (22-29 mEq/L); creatinine, 6.3 mg/dL (0.6-0.9 mg/dL); blood urea nitrogen, 50 mg/dL (6-21 mg/dL); calcium, 16.3 mg/dL (8.9-10.1 mg/dL); and phosphorus, 4.1 mg/dL (2.5-4.5 mg/dL). A catheter urine specimen revealed gram-negative bacilli and 1 to 3 white blood cells per high-power field.

1. Which <u>one</u> of the following is the <u>most likely</u> cause of this patient's somnolence and confusion?

a. *Urosepsis*
b. *Alcohol withdrawal*
c. *Acute renal failure (ARF) with dehydration*
d. *Hypercalcemia*
e. *Intracranial mass*

Although urosepsis frequently causes altered mental status, it is unlikely in the absence of fever, leukocytosis, dysuria, flank or abdominal pain, and significant pyuria. Long-term alcohol use can also cause dizziness and confusion. Considering the patient's history of daily alcohol consumption, she should be monitored for acute withdrawal, but her apathy, somnolence, and stable vital signs argue against alcohol withdrawal syndrome. Acute renal failure can cause uremic encephalopathy and distal polyneuropathy, but these typically present with headache, tremor, asterixis, and hyperreflexia,[2] none of which were evident here. In contrast, although hypercalcemia is not among the most common causes of abrupt mental status changes, it would account for the patient's symptoms. Severe hypercalcemia, with serum calcium levels exceeding 14 mg/dL, produces nausea, lethargy, confusion, weakness, abdominal pain and dyspepsia (for which the patient was taking an over-the-counter calcium carbonate antacid), and dehydration. These symptoms would not be explained by an intracranial mass, which would likely manifest with focal neurologic deficits rather than symmetric distal neuropathy.

On admission, electrocardiography showed a normal sinus rhythm, and chest radiography revealed mild interstitial infiltrates of the middle and lower lung fields.

2. Which <u>one</u> of the following would be the <u>most appropriate</u> first step in this patient's management?

a. *Transfuse packed red blood cells*
b. *Infuse 0.9% normal saline (NS)*
c. *Administer hydrocortisone*
d. *Administer pamidronate*
e. *Initiate hemodialysis*

This patient presented with severe hypercalcemia, anemia, ARF, and dehydration. Blood transfusion is a reason-

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See end of article for correct answers to questions.

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able consideration on the basis of current guidelines, which recommend transfusion when hemoglobin concentration is less than 7.0 g/dL in hemodynamically stable patients with end-organ ischemia.[3] Our patient presented with a hemoglobin concentration of 7.0 g/dL, but because she was stable, transfusion could be deferred until appropriate cross match blood became available. In contrast, fluid resuscitation should not be delayed because it is the optimal treatment for all of the presenting problems, which include hypercalcemia, ARF, hypovolemia, and hemorrhage. In hypercalcemic patients, crystalloid fluids facilitate renal calcium excretion and reverse intravascular volume depletion induced by hypercalcemic nephrogenic diabetes insipidus. Corticosteroids, bisphosphonates, and calcitonin are more useful for the nonemergent management of hypercalcemia because their effects are not realized immediately. Hemodialysis with low-calcium dialysate, which is used almost exclusively in patients who cannot tolerate aggressive fluid resuscitation, would not be indicated here.[4]

A continuous infusion of NS was initiated at the rate of 300 mL/h, titrated to achieve a urine output of 150 mL/h. Once euvolemia was achieved and the patient's calcium level decreased to 13 mg/dL, she was also given furosemide (20 mg/d intravenously on hospital days 1-3), pamidronate (15 mg intravenously once on hospital day 3), and salmon calcitonin (3 doses of 360 U subcutaneously on hospital days 3 and 4). By hospital day 5, the patient's serum calcium level had decreased to 9.1 mg/dL, and NS was discontinued. Three units of packed red blood cells were transfused on hospital days 2 and 3, with an appropriate increase in hemoglobin concentration to 9.2 g/dL.

3. Given the clinical data available thus far, which <u>one</u> of the following is the <u>most likely</u> etiology of hypercalcemia in this patient?

a. *Hyperparathyroidism*
b. *Immobility*
c. *Sarcoidosis*
d. *Malignancy*
e. *Medications*

The most common cause of mild or moderate hypercalcemia in the general population, particularly in the outpatient setting, is primary hyperparathyroidism. However, calcium levels rarely exceed 14 mg/dL or cause symptoms, making this diagnosis plausible but unlikely.[5] Prolonged immobilization is an infrequent cause of hypercalcemia and occurs in the setting of high bone turnover, as in patients with Paget disease. Our patient had neither prolonged immobilization nor evidence of high bone turnover. Hypercalcemia can also be caused by elevated calcitriol levels associated with granulomatous disorders, such as sarcoidosis. Nonetheless, it is unlikely in our patient because she had no cough, dyspnea, chest pain, or diagnostic hilar adenopathy on chest radiography.

In contrast, the most common cause of *severe* hypercalcemia in the general population is malignancy. In our patient, the possible diagnosis of cancer is supported by the long-standing history of smoking, weight loss, infiltrates on chest radiography (possible lung cancer), alcohol use (possible liver cancer), dyspepsia (possible gastric or esophageal cancer), and vaginal bleeding (possible gynecologic malignancy). Severe hypercalcemia also can occasionally be the result of medical toxicity. The patient reported a long-standing history of calcium carbonate use, which is one of several agents associated with hypercalcemia in otherwise healthy adults.[6] However, medication-induced hypercalcemia is less common than malignancy-associated hypercalcemia, particularly among patients with additional symptoms that arouse concern for the presence of malignancy. The weight loss supplement taken by the patient did not contain calcium or calcimimetics and has not been reported to cause hypercalcemia.[1]

Subsequent diagnostic work-up was negative for primary hyperparathyroidism, sarcoidosis, and malignancy. The patient's parathyroid hormone (PTH) was appropriately suppressed, and PTH-related peptide, one of the triggers of malignancy-associated hypercalcemia, was undetectable. Angiotensin-converting enzyme, occasionally elevated in patients with sarcoidosis, was normal at 49 U/L (8-53 U/L) despite an elevated creatinine level (6.2 mg/dL). Levels of 1,25-dihydroxyvitamin D [$1,25(OH)_2D$] and vitamin A were low, at less than 8.0 pg/mL (22-67 pg/mL) and 120 μg/L (360-1200 μg/L), respectively. No malignancy or significant adenopathy was detected on computed tomography of the chest, abdomen, and pelvis; magnetic resonance imaging of the head and neck; ultrasonography of the retroperitoneum and pelvis; and serum and urine protein electrophoreses. Esophagogastroduodenoscopy revealed erosive gastropathy consistent with nonsteroidal anti-inflammatory drug (NSAID) use, but gastric biopsy revealed no malignancy.

4. Which <u>one</u> of the following is the <u>principal</u> cause of this patient's renal insufficiency?

a. *Inadequate fluid intake*
b. *NSAID use*
c. *Hypercalcemia*
d. *Rhabdomyolysis*
e. *Obstruction*

Multiple factors likely contributed to this patient's renal insufficiency. She was clinically dehydrated at the time of admission, which raises concern for hypovolemic ARF. However, the severity of her renal injury, with an estimated glomerular filtration rate of 7 mL/min per 1.73 m^2 (>60 mL/min per 1.73 m^2), is inconsistent with the clinical estimate of mild

volume loss as evidenced by the absence of hypotension, tachycardia, and hemodynamic instability. Ibuprofen, which the patient was taking on a long-term basis for low back pain, likely exacerbated her renal failure. However, clinically relevant NSAID-induced renal dysfunction would present with abnormal findings on urinalysis, including granular casts, muddy brown casts, renal epithelial cells (with acute tubular necrosis), or eosinophils (with acute interstitial nephritis), and none of these were detected. The most likely primary etiology of kidney injury in this patient is hypercalcemia, which causes direct renal vasoconstriction as well as renal hypoperfusion secondary to natriuresis-induced volume contraction. Rhabdomyolysis is unlikely in the absence of myalgia, myoglobinuria, and risk factors for muscle breakdown. Similarly, obstructive nephropathy is rare in a female patient with no apparent obstructive process.

The patient's calcium level normalized after 5 days of fluid resuscitation and adjunct use of a loop diuretic, bisphosphonate, and calcitonin. On restoration of normocalcemia, her renal function improved but did not normalize (creatinine, 3.0 mg/dL; blood urea nitrogen, 20 mg/dL; and estimated glomerular filtration rate, 35 mL/min per 1.73 m^2). The patient's clinical course supports the presumed diagnosis of hypercalcemia-induced ARF, because improvement in renal function is expected to lag behind resolution of hypercalcemia and may be incomplete. Failure of NS to fully restore kidney function argues against purely hypovolemic ARF, and some improvement due to rehydration is inconsistent with both NSAID-induced and obstructive nephropathy.

The patient's condition stabilized, and she was discharged from the hospital with close follow-up.

5. Which <u>one</u> of the following would be the <u>most reasonable</u> approach after the patient is discharged from the hospital?

a. *Watchful waiting*
b. *Positron emission tomography*
c. *Skeletal survey*
d. *Colonoscopy*
e. *Paraneoplastic panel*

Given the patient's lack of localizing symptoms, good response to symptomatic treatment, negative findings on comprehensive hospital evaluation, and ease of close follow-up in the outpatient setting, watchful waiting was deemed appropriate. Whole-body positron emission tomography and skeletal survey should be considered only if hypercalcemia recurs or additional symptoms of potential malignancy are discovered. Colonoscopy would not be indicated in a 47-year-old patient in the absence of familial gastrointestinal disease or symptoms referable to the colon. Similarly, although a paraneoplastic panel may suggest the presence of occult malignancy, its low sensitivity and high cost argue against its use.

The patient was discharged to her home with the presumed diagnosis of milk-alkali syndrome (MAS) secondary to calcium carbonate ingestion. Although a diagnosis of exclusion, MAS is the most likely diagnosis considering the patient's complete and lasting response to symptomatic therapy and to discontinuation of calcium carbonate. Because NSAIDs likely contributed to renal injury, the patient was also advised to avoid NSAID use if possible. A proton pump inhibitor, ferrous sulfate, progesterone, and an antihypertensive agent were prescribed for the patient's newly diagnosed comorbid disorders. Ten days after discharge, her laboratory values had improved to the following: hemoglobin, 10.3 g/dL; calcium, 9.9 mg/dL; and creatinine, 1.6 mg/dL. Confusion and dizziness had resolved, and weakness and lower-extremity hyperesthesia were significantly improved. Seven months after discharge, she continued to abstain from calcium carbonate and ibuprofen, and her laboratory values remained stable, with a calcium level of 9.8 mg/dL and a creatinine level of 0.9 mg/dL, reaffirming the initial presumptive diagnosis of calcium carbonate toxicity.

DISCUSSION

Calcium homeostasis is maintained by a redundant system of PTH, vitamin D, and calcitonin acting at multiple target organs, including bone, kidneys, and the gastrointestinal tract. As ionized (free, metabolically active) calcium levels decrease, the parathyroid glands secrete PTH, which raises calcium levels by stimulating bone resorption, renal calcium reabsorption, phosphate excretion, and renal $1,25(OH)_2D$ synthesis. Vitamin D, in turn, promotes bone resorption, increases intestinal absorption of dietary calcium and phosphate, and inhibits PTH secretion. Finally, calcitonin, released by parafollicular cells of the thyroid in response to hypercalcemia, has been shown to transiently inhibit bone resorption.[4]

In the ambulatory setting, hypercalcemia is typically mild, asymptomatic, and detected incidentally during routine laboratory screening. The most common cause of mild hypercalcemia, as well as hypercalcemia diagnosed in the outpatient setting, is primary hyperparathyroidism. Most patients have single (85%) or multiple (5%) benign parathyroid adenomas, and 10% have diffuse parathyroid hyperplasia; parathyroid adenocarcinoma is extremely rare. In contrast, severe, symptomatic hypercalcemia (calcium >4 mg/dL) is more prevalent among hospitalized patients and is typically the result of underlying malignancy. It is estimated that 20% to 30% of patients with cancer will develop hypercalcemia during the course of their illness, which can occur by 1 of 4 distinct mechanisms. Most patients (80%) present with humoral hypercalcemia of malignancy (HCM), caused by tumor secretion of PTH-related peptide, a functional analogue of native PTH. Although almost any malignancy can cause HCM, the

most commonly implicated cancers are renal cell carcinoma; human T-cell leukemia-lymphoma; cancers of the ovary, endometrium, and breast; and squamous cell carcinomas of the head and neck, lungs, esophagus, and cervix. Hypercalcemia of malignancy is not dependent on bone metastasis. In 20% of cancer patients, hypercalcemia results from local osteolytic hypercalcemia, a cytokine-mediated osteoclastic bone resorption adjacent to a focus of bone marrow metastasis. This is seen in multiple myeloma, lymphoma, and metastatic breast cancer. Finally, less than 1% of cancer-associated hypercalcemia is due to hypervitaminosis D (most often in lymphoma) or ectopic PTH secretion. Importantly, irrespective of the mechanism, HCM develops when the primary disease is advanced and clinically apparent. Occult malignancy is rare, except in cases of small islet cell tumors or pheochromocytomas.[6]

Medication toxicity is another but less common cause of severe symptomatic hypercalcemia. Its prevalence continues to increase because patients are taking more calcium-containing medications. The most commonly implicated agents are supplemental calcium (calcium carbonate and calcium gluconate), vitamins A and D, lithium, and thiazide diuretics. Calcium carbonate, an over-the-counter antacid and dietary supplement, is a source of both calcium and absorbable alkali, which allows calcium to be readily absorbed and potentially triggers profound hypercalcemia via MAS.[7,8] As seen in the clinical vignette, MAS is a clinical triad of hypercalcemia, metabolic alkalosis (absolute or relative), and renal insufficiency that occurs in the setting of calcium and alkali consumption and no other identifiable causes of hypercalcemia. Although patients with underlying kidney disease are at increased risk of developing MAS, it is also seen in otherwise healthy persons. Renal failure in MAS is generally reversible if diagnosed early; however, chronic hypercalcemia can produce permanent kidney injury via metastatic calcification of renal parenchyma. Remarkably, most published cases of MAS occurred with modest daily calcium carbonate ingestion of less than 2000 mg/d, whereas the maximum recommended dose of calcium carbonate is 7000 mg/d.[9]

Additional causes of moderate to severe hypercalcemia that may be encountered in general practice include the many granulomatous diseases, such as sarcoidosis, tuberculosis, leprosy, coccidiomycosis, and histoplasmosis. These produce hypervitaminosis D vis-à-vis unregulated $1,25(OH)_2D$ production by granuloma macrophages. High $1,25(OH)_2D$ levels cause hypercalcemia indirectly, although endogenous PTH is appropriately suppressed.[4] Even rarer causes of hypercalcemia are hyperthyroidism, immobilization in high bone turnover states, pancreatitis, and familial hypocalciuric hypercalcemia.[4]

Treatment of hypercalcemia should be directed both at controlling symptoms and correcting the underlying pathology. Immediate relief is provided by rapid and aggressive volume expansion with an isotonic crystalloid, such as NS; however, a loop diuretic may be cautiously added in patients with signs of volume overload after euvolemia is restored. Symptomatic patients who cannot tolerate hydration should undergo urgent hemodialysis with calcium-free dialysate. Bisphosphonates are often given early, particularly to patients with HCM; however, because their effects are not appreciated for several days, they are not an emergent treatment modality. Calcitonin provides transient relief but is associated with a relatively high incidence of allergic reactions, tachyphylaxis, and other adverse effects. Finally, corticosteroids are beneficial in the treatment of vitamin D–associated hypercalcemia but are generally not administered early in the emergent setting.[4,7,10]

In conclusion, severe hypercalcemia accounts for up to 3% to 5% of hospital admissions.[5] Symptomatic patients require emergent and aggressive volume resuscitation, followed by judicious use of loop diuretics, bisphosphonates, glucocorticoids, calcitonin, and/or hemodialysis. Symptomatic treatment should be continued while the etiology of hypercalcemia is established, with ultimate transition to targeted therapy. Most patients with total calcium exceeding 14 mg/dL have a clinically apparent malignancy or history of taking medications precipitating calcium excess. In contrast, primary hyperparathyroidism is a common cause of mild hypercalcemia seen in the outpatient setting. Because medication toxicity has been noted to be an increasingly prevalent cause of severe hypercalcemia, it should be considered in all patients without an apparent neoplastic process. Medication-induced hypercalcemia is often self-limited and resolves with symptomatic therapy and discontinuation of the offending agent.

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Correct answers: 1. *d*, 2. *b*, 3. *d*, 4. *c*, 5. *a*