A 56-year-old woman presented to an outside emergency department with a history of several years of chronic symptoms including fatigue, weakness, and malaise. The patient had experienced abdominal discomfort and diminished appetite with some unintentional weight loss. She also reported diffuse myalgias and arthralgias that have been progressively worsening in severity.

On medical review, the patient was taking no medications. She had a past medical history of treated hepatitis C, obesity, and anxiety with panic attacks. Past surgical history included laparoscopic gastric banding and breast augmentation. Vitals signs were within normal limits. Physical examination was notable for temporal muscle wasting and dry mucous membranes. The remainder of the physical examination findings were normal, including appearing without acute distress and being alert and oriented with appropriate affect. Heart examination showed regular rate and rhythm, no murmurs, normal jugular venous pressure, and no peripheral edema. Lungs were clear to auscultation bilaterally with normal respiratory rate and no respiratory distress. Abdomen was soft, nontender, and nondistended.

Initial laboratory work was notable for an overall normal basic metabolic panel, except for the following (reference ranges provided parenthetically): serum calcium, 18.0 mg/dL (8.6 to 10.0 mg/dL); bicarbonate, 34 mg/dL (22 to 29 mg/dL); and serum creatinine, 1.8 mg/dL (0.59 to 1.04 mg/dL). Phosphorus concentration was normal at 2.6 mg/dL (2.5 to 4.5 mg/dL). A complete blood count and hepatic function panel were within normal limits.

1. Which of the following is the most likely cause of hypercalcemia in this patient?
   a. Milk-alkali syndrome
   b. Familial hypocalciuric hypercalcemia
   c. Surreptitious thiazide use
   d. Hyperthyroidism
   e. Hypercalcemia of malignancy

   Milk-alkali syndrome is classically caused by excess ingestion of calcium carbonate, leading to a triad of hypercalcemia, metabolic alkalosis, and acute kidney injury.1-4 Its occurrence is associated with antacid use for peptic ulcer disease and calcium supplementation for osteoporosis. Although this patient’s elevated serum bicarbonate and creatinine levels are suggestive of milk-alkali syndrome, the patient does not report taking calcium-containing products, nor does she have a medical condition associated with their use, making it an unlikely etiology.

   Familial hypocalciuric hypercalcemia stems from a genetic mutation in the calcium-sensing receptor, which decreases sensitivity to high levels of extracellular calcium.1-4 This leads to inadequate suppression of parathyroid hormone (PTH) secretion and excessive renal reabsorption of calcium, inducing both hypercalcemia and hypocalciuria. In addition to being a relatively rare cause of mild hypercalcemia, our patient had no personal or family history of hypercalcemia.

   Surreptitious thiazide diuretic use is possible in this patient, given her history of laparoscopic gastric banding and ongoing obesity, as a means of immediate weight loss. It can increase serum calcium levels, but it also causes other electrolyte abnormalities, such as hyponatremia and hypokalemia, which is not consistent with this patient’s initial laboratory work.
Hyperthyroidism classically is manifested with a constellation of symptoms, such as increased frequency of bowel movements, dyspnea, palpitations, tremor, and heat intolerance. It can also cause hypercalcemia through thyroid hormone–inducing increased bone resorption, but our patient’s presentation is less consistent with hyperthyroidism.

Primary hyperparathyroidism and malignant disease are the two most common causes of hypercalcemia, accounting for 90% of all cases.\textsuperscript{1-4} Primary hyperparathyroidism from parathyroid adenoma or hyperplasia usually causes milder hypercalcemia. Cases of severely elevated serum calcium, such as in this patient, are particularly concerning for malignant disease. In addition, the patient’s constitutional symptoms of weight loss, fatigue, and malaise warrant evaluation for malignant disease. Hypercalcemia of malignancy can be due to several different mechanisms, including a paraneoplastic process with PTH-related protein secretion from the tumor, local osteolytic activity, and overexpression of 1α-hydroxylase causing increased conversion of calcidiol to calcitriol.

Treatment of severe hypercalcemia was initiated in the emergency department with intravenous (IV) fluids and bisphosphonates.

2. In addition to the aforementioned therapies, which of the following would be most appropriate to include as part of the initial treatment of this patient?
   a. Calcitonin
   b. Furosemide
   c. Glucocorticoids
   d. Denosumab
   e. Hemodialysis

   Treatment of severe hypercalcemia generally occurs on an inpatient basis and includes IV fluids, bisphosphonates, and calcitonin.\textsuperscript{1-4} The administration of several liters of isotonic IV fluids can treat underlying dehydration caused by hypercalcemia-induced nephrogenic diabetes insipidus. By restoring intravascular volume, it therefore lowers the relative and absolute serum calcium levels through dilution and facilitation of renal calcium clearance, respectively. However, it carries the risk of fluid overload, particularly in patients with congestive heart failure or kidney disease. Bisphosphonates reduce calcium levels by inhibiting bone resorption from osteoclasts. In patients with renal impairment, particularly with creatinine clearance between 30 and 35 mL/min, the use of bisphosphonates is not recommended. It can be nephrotoxic, primarily based on how quickly it is administered, as it can cause nephrotic-range proteinuria and acute kidney injury with a risk of progression to dialysis, but this is more likely in patients with multiple myeloma. Injury can be mitigated in most cases by adequate hydration before administration and slow infusion rates. Calcitonin has rapid hypocalcemic effect by reducing both bone resorption and renal reabsorption of calcium, but its use is limited by tachyphylaxis, which usually develops within several days of use. Furosemide or another loop diuretic is typically indicated in cases of volume overload, but it is also used to allow continued aggressive IV fluid administration to aid in the renal excretion of calcium. Although their use can increase urinary calcium excretion, loop diuretics can also worsen dehydration and other electrolyte abnormalities. Glucocorticoids are appropriate for treating hypercalcemia caused by known granulomatous disease as they inhibit the excessive conversion of calcidiol into calcitriol mediated by 1α-hydroxylase in those conditions. Denosumab works by binding RANK ligand and inhibiting osteoclast activity; it is typically used in patients with hypercalcemia of malignancy or those in whom bisphosphonate use is contraindicated, but it is not usually a first-line therapy. Hemodialysis is generally reserved for patients with treatment failure of medical therapy or with life-threatening electrolyte abnormalities.

   The patient received treatment with IV fluids, bisphosphonates, and calcitonin. She was discharged after normalization of serum calcium levels and improvement in her
symptoms. After discharge, she was referred for further evaluation of her hypercalcemia to our institution, where additional diagnostic testing was performed.

3. Which of the following would be the most appropriate for initial evaluation of hypercalcemia in this patient?
   a. PTH
   b. Urinary calcium
   c. 24,25-Dihydroxyvitamin D
   d. PTH-related peptide
   e. Serum and urine protein electrophoresis

Parathyroid hormone is among the most valuable initial tests for determining the cause of hypercalcemia, and its measurement is often recommended as the initial diagnostic step. In the setting of hypercalcemia, high PTH and nonsuppressed or “inappropriately normal” PTH levels are most commonly due to primary hyperparathyroidism. In this situation, subsequent testing for urine calcium clearance is recommended. Hypercalcemia with high PTH and low fractional urinary excretion of calcium is diagnostic for familial hypocalciuric hypercalcemia.

Low PTH in the setting of hypercalcemia suggests appropriate PTH suppression. Common causes of non–PTH-mediated hypercalcemia include malignant disease, medications (eg, excess vitamin D consumption), milk-alkali syndrome, hyperthyroidism, and granulomatous disease. Measurement of 25-hydroxyvitamin D can support a diagnosis of vitamin D intoxication from direct ingestion of vitamin D, which is available in foods or supplements in 2 main forms, D2 (ergocalciferol) and D3 (cholecalciferol). 1,25-Dihydroxyvitamin D can be elevated in hypercalcemia from granulomatous disease or exogenous supplementation of calcitriol. Recommendations for evaluation of suspected hypercalcemia of malignancy include subsequent testing for PTH-related peptide, which can be elevated in paraneoplastic syndromes. Serum and urine protein electrophoresis and measurement of serum free light chain levels are recommended to evaluate for multiple myeloma. Evaluation for malignant disease also commonly includes bone imaging and cross-sectional imaging of the chest, abdomen, and pelvis.

Extensive additional laboratory testing and imaging obtained the following values: PTH, 8.4 pg/mL (16 to 65 pg/mL); PTH-related peptide, 0.3 pmol/L (<4.2 pmol/L); 1,25-dihydroxyvitamin D, 100 pg/mL (18 to 78 pg/mL); 25-hydroxyvitamin D, 54.8 ng/mL (20 to 80 ng/mL); and angiotensin-converting enzyme, 78 U/L (16 to 85 U/L). Vitamin A levels, thyroid-stimulating hormone, free T4, cortisol, and lactate dehydrogenase were all within normal limits. Further serologic, immunologic, and rheumatologic evaluation was unremarkable. Serum and urine protein electrophoresis with immunofixation, including serum free light chain levels, did not show evidence of monoclonal gammopathy.

Computed tomography (CT) of the chest and abdomen found no clinically significant abnormalities; the breast implants were intact bilaterally. Skeletal survey found no skeletal abnormalities. Bone scintigraphy found no abnormal focus of scintigraphic activity. Bone marrow biopsy did not show evidence of plasma cell proliferative disorder, lymphoma, or granulomatous disease. Initially, no clear cause was identified for the PTH-independent hypercalcemia. After extensive evaluation, there was no evidence of malignant disease. Low PTH with high 1,25-dihydroxyvitamin D was suggestive of a granulomatous disorder, but the patient appeared to lack evidence of an associated underlying condition, such as tuberculosis, sarcoidosis, lymphoma, or polyangiitis with granulomatosis.

Additional history taking with the patient revealed a 5-year history of repeated cosmetic silicone injections into the lips and buttocks. Physical examination of the buttocks was notable for nodularity bilaterally. These findings were concerning for hypercalcemia due to a granulomatous disorder secondary to silicone.

4. Which of the following tests would most conclusively confirm this suspected diagnosis?
   a. C-reactive protein
b. 24,25-Dihydroxyvitamin D
c. Soft tissue biopsy
d. Dual-energy X-ray absorptiometry scan
e. Renal ultrasound

C-reactive protein levels have not been shown to be associated with silicone granuloma disease, so testing for C-reactive protein would not be of diagnostic value. 24,25-Dihydroxyvitamin D is an inactive metabolite of vitamin D and is measured in cases of PTH-independent hypercalcemia with elevated 1,25-hydroxyvitamin D, as also found in this patient. However, it is the result of a loss of function mutation in the CYP24A1 gene that helps regulate the concentration of active vitamin D metabolites, rather than granulomatous disease. Biopsy of the suspected silicone granuloma would best be able to confirm the diagnosis through finding certain characteristic histopathologic features. A dual-energy X-ray absorptiometry scan is a useful screening tool for osteoporosis secondary to hypercalcemia, and renal ultrasound is a useful screen for nephrolithiasis, but neither would definitively diagnose granulomatous disease or be indicated as part of an evaluation for it.

The patient underwent positron emission tomography—CT imaging, which showed diffuse hypermetabolism in the subcutaneous tissues of the bilateral gluteal regions, consistent with cosmetic injections. Biopsy of the soft tissue of the gluteal region showed histologic changes consistent with silicone granuloma, including organizing fat necrosis associated with foreign body giant cell reaction.

5. For this diagnosis, which of the following would be the best initial treatment?
   a. Hydroxychloroquine
   b. Etanercept
   c. Minocycline
   d. Prednisone
   e. Surgical débridement

A corticosteroid, such as prednisone, is the most appropriate first-line, pharmacologic treatment of hypercalcemia in granulomatous disease. Hypercalcemia may be reduced with the use of corticosteroids as they inhibit production of calcitriol in activated macrophages. However, not all patients respond to corticosteroid use, and long-term corticosteroid use is associated with significant morbidity.

Immunosuppressant medications, such as hydroxychloroquine and etanercept, have been used in cases of silicone-induced granulomas as well as in hypercalcemia secondary to sarcoidosis. They are used for their anti-inflammatory effects, but they are more so used if corticosteroid therapy failed or led to intolerable adverse effects or following a corticosteroid taper.

An alternative treatment option would be minocycline, a tetracycline antibiotic, successful use of which has been reported in several patients. Its mechanism of action in granulomatous disorders is purportedly related to its anti-inflammatory effect.

Surgical débridement is an option for definitive treatment, but surgery is not feasible in many patients because of the extensive distribution of silicone as well as migration.

A 2-pronged approach was used to address the patient’s silicone-induced hypercalcemia. After recovery of the patient’s kidney function, zoledronic acid was started to treat her hypercalcemia but was discontinued after it failed to lower the patient’s serum calcium levels. For treatment of the granulomatous disease, the patient was started on oral prednisone, 20 mg/d. By 1-month follow-up, there had been a reduction in serum calcium, but it remained in the elevated range. The prednisone dose was then increased to 40 mg/d. This led to normalization of serum calcium and calcitriol levels. To avoid adverse effects associated with long-term systemic corticosteroid use, the patient was subsequently prescribed a steroid taper and transitioned to hydroxychloroquine. She continues to follow up with the endocrinology clinic.

DISCUSSION

This case features a patient with classic signs and symptoms of hypercalcemia, including...
fatigue, weakness, abdominal discomfort, anorexia, weight loss, and dehydration. She was treated acutely with IV fluids, bisphosphonates, and calcitonin. Further evaluation found the severe hypercalcemia to be non–PTH mediated, which was particularly concerning for malignant disease, but extensive laboratory and imaging evaluation did not find supporting evidence. The high 1,25-dihydroxyvitamin D and angiotensin-converting enzyme levels were suggestive of granulomatous disease, which was eventually supported by further history taking that revealed cosmetic silicone injections and examination with palpable nodularity. Positron emission tomography–CT found hypermetabolic activity in the gluteal region, and biopsy confirmed silicone granuloma.

Hypercalcemia with low PTH and elevated 1,25-dihydroxyvitamin D, as in this patient, warrants work-up for malignant neoplasia and granulomatous disease. Patients with lymphoma or granulomatous disease usually have clinically evident disease on evaluation.1-4 If evidence of an obvious cause, such as lymphoma or sarcoidosis, is not found, a systematic search for occult granulomas (renal, hepatic, bone marrow) is indicated.

Liquid injectable silicone is available in the United States in products that are Food and Drug Administration approved for treating retinal detachment, with off-label uses including cosmetic microdroplet injections. Reported complications from silicone injections include cellulitis, abscess formation, ulceration, scarring, migration, and granuloma formation.5-9

Review of the current literature revealed primarily case reports of silicone granulomas.5-9 A systematic review of multiple case reports identified the most common cause (silicone), site affected (buttock), treatment (hydration, corticosteroids, and bisphosphonates), and complication (renal failure) in patients with hypercalcemia associated with cosmetic injections.9 Multiple articles report cases of patients with granulomatous nodules secondary to the use of cosmetic silicone injections, including in the face and buttocks. Granuloma formation has also been reported after rupture of silicone breast implants. The time between silicone injection and symptom onset can be between a few months and several years. Complications such as granulomatous reaction may be more common with non–medical-grade silicone and injection by unlicensed practitioners. The pathophysiologic mechanism of granulomatous reaction to silicone is thought to include the natural foreign body response by macrophages as well as possibly being triggered by infections or trauma.

Clinicians should be aware of these possible complications of cosmetic silicone injections, including granulomatous disease, to be able to evaluate for them when taking history and performing a physical examination.

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REFERENCES

CORRECT ANSWERS: 1. e. 2. a. 3. a. 4. c. 5. e.