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64-Year-Old Woman With General Malaise and Hypercalcemia

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See end of article for correct answers to questions.

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A 64-year-old woman was admitted to the hospital for electrolyte derangements and acute kidney injury after presenting to the emergency department with a 2-week history of general malaise. Her medical history was notable for type 2 diabetes, hypertension, and hyperlipidemia. During the 2 weeks leading up to hospital admission, the patient had progressively worsening symptoms of weakness, fatigue, and decreased appetite. She reported subjective fevers but no chills, sweats, or weight loss. Her only other notable symptoms included nausea without emesis and worsening of chronic hip and low back pain. Her medications included ibuprofen, triamterene-hydrochlorothiazide, lisinopril, glyburide, and niacin. To alleviate the nausea, she had been taking Tums, up to 3 tablets daily, and was drinking up to 4 cups (0.96 L) of milk per day. She had a previous 10-pack-year history of smoking but had quit 15 years previously. Physical examination was notable for tachycardia with heart rate in the low 100s (beats/min), but no signs of volume depletion were detected. Laboratory studies revealed the following (reference ranges provided parenthetically): total calcium, 14.1 mg/dL (8.9-10.1 mg/dL); ionized calcium, 6.97 mg/dL (4.65-5.30 mg/dL); creatinine, 1.8 mg/dL (her baseline creatinine level was 0.8-0.9 mg/dL); phosphorus, 3.8 mg/dL (2.5-4.5 mg/dL); and albumin, 3.6 g/dL (3.5-5.0 g/dL). Electrocardiography detected no interval changes and was notable only for sinus tachycardia.

1. Which *one* of the following is the *best* laboratory test to evaluate hypercalcemia?

a. Measure parathyroid hormone (PTH) level
b. 24-Hour urinary calcium excretion
c. PTH-related protein (PTHrP) measurement
d. Measure vitamin D metabolites
e. Determine thyrotropin level

The best step in evaluation at this time is to measure an intact PTH level to help distinguish between PTH-mediated and non—PTH-mediated causes of hypercalcemia.[1,2] If the PTH level is normal or high, a 24-hour urinary calcium level can be determined to help distinguish between familial hypocalciuric hypercalcemia and primary or tertiary hyperparathyroidism.[2] A low or low-normal serum intact PTH level, typically less than 25 pg/mL when assuming a normal range of 10 to 65 pg/mL, points toward a non—PTH-mediated cause for hypercalcemia.[3] In this case, PTHrP level, vitamin D metabolites, and other endocrinopathies can be evaluated next.[3]

Our patient's PTH measurement revealed a level of 15 pg/mL (15-65 pg/mL). The PTHrP level was 0.3 pmol/L (<2.0 pmol/L). Vitamin D metabolites were checked, including 1,25-dihydroxyvitamin D level, which was 33 pg/mL (18-78 pg/mL), and total 25-hydroxyvitamin D level, which was 26 ng/mL (20-50 ng/mL). The 24-hour urinary calcium excretion was measured during hospitalization and was within the normal range. The thyrotropin level was 1.9 mIU/L (0.3-4.2 mIU/L), serum angiotensin-converting enzyme level was less than 5 U/L (8-53 U/L), lactate dehydrogenase (LDH) level was 960 U/L (122-222 U/L), and the erythrocyte sedimentation rate was 99 mm/h (0-29 mm/h).

2. These findings, along with the laboratory results obtained on presentation, suggest which *one* of the following as the *most likely* cause of this patient's hypercalcemia?

a. Primary hyperparathyroidism
b. Malignancy-related hypercalcemia
c. Familial hypocalciuric hypercalcemia
d. Vitamin D toxicity
e. Granulomatous disease

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The patient's work-up revealed a PTH level of 15 pg/mL, which is on the low end of normal. As mentioned previously, low serum PTH concentrations (<25 pg/mL) should lead one to suspect non–PTH-mediated mechanisms as the cause of the hypercalcemia. Furthermore, primary hyperparathyroidism typically causes only mild hypercalcemia, and the serum calcium concentration rarely increases above 13 mg/dL.[1,2] This, along with the elevated LDH level and erythrocyte sedimentation rate, makes malignancy-related hypercalcemia the most likely option. Familial hypocalciuric hypercalcemia is a rather rare disorder caused by a loss of function mutation in the calcium-sensing receptor.[3] It is a benign disorder, and we would expect to see a normal or high PTH level with a very low 24-hour urinary calcium level and a low calcium to creatinine clearance ratio.[2,3] Vitamin D toxicity would be associated with a suppressed PTH level and elevated levels of vitamin D metabolites.[2] Granulomatous disease can also elevate vitamin D metabolite levels, and the serum angiotensin-converting enzyme level can also be elevated in this setting.[2]

The patient was treated with intravenous fluids, calcitonin, and one dose of zolendronic acid. Her calcium level returned to normal at 9.6 mg/dL and remained stable with oral hydration. The creatinine concentration returned to her baseline level of 0.9 mg/dL. She was discharged from the hospital with plans for further work-up for suspected malignancy in the outpatient setting. Three weeks later while being seen in clinic, she reported continued weakness and fatigue as well as abdominal pain. Her creatinine level had increased to 2.1 mg/dL, and she was referred to the hospital for admission. Additional laboratory tests revealed the following: potassium, 5.4 mmol/L (3.6-5.2 mmol/L); ionized calcium, 5.50 mg/dL; phosphorus, 4.3 mg/dL; uric acid, 12.3 mg/dL (2.7-6.1 mg/dL); lactate, 5.0 mmol/L (0.6-2.3 mmol/L); and LDH, 1340 U/L. Computed tomography (CT) of the abdomen and pelvis revealed multiple large retroperitoneal lymph nodes as well as bilateral hydronephrosis, likely secondary to ureteral compression from the lymphadenopathy. No obvious mass or other etiology for abdominal pain was identified.

3. To prevent tumor lysis syndrome, which *one* of the following should be the *next* step?

a. Correct electrolyte imbalances
b. Administer sodium bicarbonate
c. Consult nephrology for dialysis
d. Administer a hypouricemic agent and intravenous normal saline
e. Diuresis with furosemide

Tumor lysis syndrome (TLS) is an oncologic emergency due to the lysis of malignant cells and should be considered in the differential diagnosis of any patient with high malignancy burden, acute kidney injury, and electrolyte derangements. For patients at high risk for TLS or with high uric acid levels (>8 mg/dL), prophylactic measures should be initiated.[4,5] In asymptomatic patients, correction of electrolyte derangements seen with TLS, such as hypocalcemia, hyperkalemia, and hypophosphatemia, is generally not recommended unless levels are severely abnormal.[4,5] Urine alkalization with sodium bicarbonate to promote excretion of uric acid was historically recommended as part of TLS management, but currently this practice is controversial and some sources even recommend against it.[4,5] Indications for renal replacement and urgent nephrology consultation include severe oliguria or anuria, intractable fluid overload, persistent hyperkalemia, calcium-phosphate product of 70 mg^2/dL^2 or higher, or symptomatic hypocalcemia.[5] The first and most important step for the treatment or prevention of TLS is aggressive hydration with intravenous fluids and initiation of hypouricemic agents, such as allopurinol or rasburicase.[4,5] Diuretics such as furosemide or mannitol may be required to maintain adequate urine output but are contraindicated in patients with evidence of obstructive uropathy or hypovolemia.[4,5]

The patient was admitted to a medicine service, and intravenous fluids were administered for aggressive hydration. She was then given a loading dose allopurinol. Laboratory studies for markers of tumor lysis were performed every 6 hours. On further review of systems, our patient described having 2 episodes of vaginal bleeding the morning of her hospital presentation. She only noted one other episode of postmenopausal

bleeding, which had occurred 3 months before presentation. This event had been self-limited and subsequently was never investigated. The patient had had normal results of a Papanicolaou test 2 years previously and had no history of abnormal Papanicolaou test results.

4. Which *one* of the following should be the *next* step for evaluation of postmenopausal bleeding?

a. Complete blood cell count
b. Pelvic examination
c. Transvaginal ultrasonography
d. Endometrial biopsy
e. Dilation and curettage

Typically, laboratory tests are not helpful in the initial evaluation of postmenopausal bleeding (PMB). However, a complete blood cell count may be obtained if the bleeding is heavy and prolonged or if symptoms suggestive of anemia are present.[6] The best initial step in the work-up of PMB is a thorough history and physical examination, including a pelvic examination.[6-8] Oftentimes, pelvic examination findings are normal, so further investigation should follow to exclude endometrial cancer with either transvaginal ultrasonography or endometrial biopsy.[6] Dilation and curettage was the criterion standard for investigation of PMB in the past, but it should only be used if in-office methods cannot be performed.[8]

Pelvic examination of our patient revealed an enlarged, friable-appearing cervix with increased vascularity on the surface. Bimanual examination revealed a firm, fixed and nodular cervix. A Papanicolaou test was performed; however, endometrial biopsy could not be obtained at time of examination because of severe stenosis of the cervical os. Papanicolaou smear cytology revealed epithelial cell abnormality, suggestive of an invasive carcinoma. Testing was negative for human papillomavirus. Magnetic resonance imaging of the pelvis revealed a large pelvic mass, likely originating from the cervix, with bilateral parametrial extension causing bilateral ureteral obstruction and subsequent hydronephrosis. Diffuse omental carcinomatosis and pelvic and retroperitoneal lymphadenopathy were also noted. All findings prompted pelvic examination under anesthesia to obtain a cervical biopsy. Bilateral ureteral stents were placed at time of biopsy to alleviate the hydronephrosis. The pathologic findings were consistent with a diagnosis of small cell carcinoma of the cervix.

5. Which *one* of the following is the *next* step in management?

a. Positron emission tomography—CT of the chest, abdomen and pelvis
b. Head imaging with CT or magnetic resonance imaging
c. Gynecologic oncology consultation for radical hysterectomy
d. Radiation oncology consultation for initiation of pelvic radiation
e. Medical oncology consultation for initiation of chemotherapy

Small cell neuroendocrine carcinoma of the cervix is a rare gynecologic malignancy accounting for only 0.5% to 5% of all cases of cervical cancer.[9] This malignancy is quite aggressive and has propensity to present with metastases. Early staging is therefore important after histologic disease confirmation.[10] As with other cervical cancers, staging is clinical rather than surgical. Use of the International Federation of Gynecology and Obstetrics guidelines, which are based largely on physical examination, cervical biopsy, and imaging studies to determine extent of disease burden, is preferred.[10] Computed tomography or PET-CT can therefore play a helpful role for staging.[10] Although small cell carcinoma of the cervix can be associated with cranial metastases, routine imaging of the head is not recommended at time of diagnosis unless the patient has symptoms suggestive of central nervous system involvement.[10] Because of the rarity of this disease, there are few data supporting a consensus for optimal treatment strategies; however, most experts agree that multimodality treatment offers the best outcomes.[9,10] Radical hysterectomy with regional lymphadenectomy typically only has a role for patients with early-stage disease.[10] Treatment with chemoradiation is a reasonable approach for patients with advanced disease or for those who are not candidates for surgery.[10] There is no consensus regarding treatment regimen, but findings from some studies suggest that platinum-based combination chemotherapy yields improved survival, and etoposide-cisplatin is often used.[9,10]

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PET-CT was performed and revealed diffusely metastatic disease, including extensive lymphadenopathy as well as liver and osseous metastases. The patient was transferred to a medical oncology service. Given the extent of her disease burden, chemotherapy with carboplatin and etoposide was initiated. She has since undergone 4 cycles of chemotherapy, and interval PET-CT revealed marked improvement.

DISCUSSION

Although this patient's underlying diagnosis proved to be a rare disease, her presentation served as a reminder to review several scenarios that are frequently encountered in medicine. The etiology of this patient's hypercalcemia was initially unclear, but malignancy soon became a concern, and readmission to the hospital expedited her work-up. Further evaluation of this patient's PMB redirected the differential diagnosis and led to a confirmed diagnosis.

The first step in evaluating a patient with an elevated total serum calcium level is to calculate the corrected calcium value with an albumin level and/or measure an ionized calcium level in order to confirm hypercalcemia.[1] The next step is to obtain an intact PTH level to distinguish between PTH-mediated and non—PTH-mediated causes of hypercalcemia, such as malignancy, vitamin D toxicity, or granulomatous disease.[1,2] Primary hyperparathyroidism and malignancy account for more than 90% of all cases of hypercalcemia.[2] Most often, the etiology will be primary hyperparathyroidism, but in the setting of unexplained non—PTH-mediated hypercalcemia, malignancy should always be considered in the differential diagnosis.[1,2] Severe hypercalcemia, defined by calcium levels of 14 mg/dL or greater, should also lead one to suspect malignancy.[1,2] Malignancy-related hypercalcemia can be divided into at least 4 major categories: PTHrP-related, osteolytic-related, 1,25-dihydroxyvitamin D—secreting lymphomas, and ectopic hyperparathyroidism.[1] Up to 30% of patients with cancer have hypercalcemia at some point during the course of their disease.[1]

There should always be a high index of suspicion for TLS in patients presenting with metabolic derangements such as hyperuricemia, hyperkalemia, hyperphosphatemia, or hypocalcemia, as this is an oncologic emergency.[4,5] Clinical manifestations of significant toxicity due to TLS include acute kidney injury, cardiac arrhythmias, and seizures.[5] Tumor lysis syndrome is typically seen in patients with hematologic malignancies after the initiation of cytotoxic therapy; however, it can also occur spontaneously in malignancies with a high proliferative rate or in the setting of a large tumor burden.[4,5] Patients with preexisting hyperuricemia, urinary tract obstructions, dehydration, and renal insufficiency may be predisposed to development of TLS.[4] The cornerstone of treatment and prevention of tumor lysis is intravenous fluids. Initially, patients should receive approximately 2 to 3 L/m^2 per day or about 2 to 4 times normal daily maintenance fluids, with a goal of maintaining urine output of 3 mL/kg per hour.[4,5] The goal is to improve renal blood flow and glomerular filtration in order to promote excretion of uric acid and phosphate into the urine.[4,5] Care should be taken to monitor volume status, especially in patients with heart failure. Hypouricemic agents are also of benefit. Allopurinol is a competitive inhibitor of xanthine oxidase and blocks conversion of purine metabolites to uric acid, effectively decreasing formation of more uric acid.[4] An alternative strategy for management of hyperuricemia is use of rasburicase, which acts as an enzyme to convert uric acid into a more water-soluble compound and promote its excretion into the urine.[4] Rasburicase is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency because severe hemolytic anemia can occur in these patients after initiation of the drug.[4] Need for urgent dialysis secondary to TLS has decreased dramatically since the introduction of rasburicase.[5]

Postmenopausal bleeding is defined as uterine bleeding that occurs at least 1 year after cessation of menstruation.[8] Causes of PMB include atrophic endometrium, hormone replacement therapy, endometrial hyperplasia, or polyps, as well as endometrial or other gynecologic cancers.[6] Any woman presenting with PMB, therefore, requires further assessment to exclude malignancy. Gynecologic examination can help to exclude vulvar or vaginal lesions, signs of trauma, cervical polyps, or dysplasia as well as distinguish bleeding from potential nongynecologic sources (eg, perineum, periurethral, perianal).[7,8] A bimanual examination can suggest an

infectious cause if cervical motion tenderness is present, ovarian neoplasm or cyst if an adnexal mass is appreciated, or uterine fibroids or tumor if there is uterine enlargement.[7] During pelvic examination, a Papanicolaou test should be performed to screen for cervical cancer.[6,7] Although most cases of PMB are due to benign causes, guidelines support further investigation with either endometrial biopsy or transvaginal ultrasonography in order to exclude malignancy.[6]

This case also illustrates the aggressive nature of small cell neuroendocrine carcinoma of the cervix, an uncommon subtype representing less than 5% of all cases of cervical cancer.[9] This malignancy has a much poorer prognosis than other cervical cancer subtypes and has a predilection for distant metastasis and nodal and lymphovascular invasion.[10] Similar to small cell carcinoma of the lung, areas of metastasis commonly include bone, brain, liver, and bone marrow.[9] Patients can also rarely present with paraneoplastic syndromes manifesting as Cushing syndrome, syndrome of inappropriate antidiuretic hormone secretion, hypercalcemia, or neurologic syndromes. Five-year survival rates have been reported to range from 30% to 40% for early-stage disease and 0% to 14% for advanced-stage disease.[11] Given the propensity of this malignancy to present with metastases, imaging with CT or PET-CT to determine the extent of disease burden should be performed after disease confirmation.[10] Disease staging is achieved using International Federation of Gynecology and Obstetrics clinical staging criteria, and extent of disease determines next steps for treatment.[9] There is a lack of standardized guidelines for optimal therapeutic strategies for this disease; however, multimodality therapy appears to offer the best outcomes.[11]

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CORRECT ANSWERS: 1. a. 2. b. 3. d. 4. b. 5. a