A SELF-TEST ON A CLINICAL CASE

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CME CREDIT

A 56-year-old man with hypercalcemia

A 56-YEAR-OLD MAN presents to the outpatient general internal medicine clinic to establish care. He is an immigrant from Guyana who has been in the United States for 9 years, during which he has not received regular medical care.

He says he has not had any significant health problems, although he has chronic intermittent mechanical low back pain and intermittent gastroesophageal reflux disease (GERD) for which he takes ranitidine 75 mg as needed, his only medication. He does not smoke cigarettes or consume alcohol. He is married with five children and works at the airport's maintenance department.

Physical examination. Weight 67 kg, pulse 94, blood pressure 146/83 mm Hg, respiratory rate 16. He appears to be his stated age; the only significant abnormality noted on examination is a palpable liver edge with an estimated normal liver span.

Routine laboratory tests. His calcium, glucose, and creatinine concentrations are elevated (TABLE 1). On additional testing, his complete blood count is normal, his alkaline phosphatase concentration is elevated at 250 U/L (normal 20–120 U/L), and his serum aspartate aminotransferase, alanine aminotransferase, and bilirubin concentrations are within normal limits.

TABLE 1
The patient's laboratory values

SUBSTANCE	PATIENT'S VALUE		NORMAL RANGE
Sodium	142	mmol/L	135–146
Potassium	3.8	mmol/L	3.5–5.0
Chloride	103	mmol/L	98–110
CO_2	29	mmol/L	24–32
Blood urea nitrogen	19	mg/dL	10–25
Creatinine	1.5	mg/dL	0.1–1.4
Glucose	167	mg/dL	65–110
Calcium	11.3	mg/dL	8.5–10.5
Albumin	4.2	g/dL	3.5–5.0

WHAT IS CAUSING THE HYPERCALCEMIA?

1 Which is the *least* likely cause of his hypercalcemia?

- ❑ Primary hyperparathyroidism
- ❑ Malignancy
- ❑ Spurious elevation of serum calcium
- ❑ Milk-alkali syndrome
- ❑ Vitamin A intoxication

Primary hyperparathyroidism and **malignancy** account for up to 90% of cases of hypercalcemia.[1] In general, outpatients without symptoms of weight loss or any other symptom suggestive of malignancy (eg, hemoptysis, prolonged cough, blood in stool) are more likely to have primary hyperparathyroidism, while hospitalized patients with symptoms are likely to have malignancy-related causes. This is actually an oversimplification, because occult malignancies can present with hypercalcemia, although rarely, and the incidence of primary hyperparathyroidism is increased in patients with a malignancy.

Malignancy can cause hypercalcemia via two mechanisms: parathyroid hormone-related peptide (PTHrP) and osteoclast activation factor (the action of which is mediated by interleukin-1 and tumor necrosis factor).[1] This patient's age, palpable hepatomegaly, and elevated alkaline phosphatase concentration

suggest that a malignancy workup should be done.

Spurious elevation of the serum calcium level can occur due to inadvertent hemoconcentration during blood collection, dehydration, or elevated serum protein concentrations. The calcium level should be measured again before proceeding with additional evaluation.[1]

Milk-alkali syndrome used to be more common in the days of the Sippy diet for peptic ulcer disease, when patients would ingest large amounts of milk and absorbable antacids such as sodium bicarbonate. It became less common with the introduction of nonabsorbable antacids, but now the syndrome is reappearing because more people are using calcium carbonate to treat osteoporosis, dyspepsia, and the hyperphosphatemia of chronic renal failure.[1] Features are hypercalcemia without hypercalciuria or hyperphosphatemia, with only mild alkalosis, normal serum alkaline phosphatase, and renal insufficiency that can vary from mild to severe.

This patient has GERD, so he may be using absorbable antacids, and milk-alkali syndrome is a possibility.

Milk-alkali syndrome is reappearing due to use of calcium carbonate

Vitamin A intoxication, a rare cause of hypercalcemia, can occur when people take 50,000 to 100,000 units of vitamin A daily—10 to 20 times the minimum daily requirement. It can raise the serum calcium level to the range of 3 to 3.5 mmol/L (12–14 mg/dL). Typical features of severe hypercalcemia such as fatigue, anorexia, and sometimes severe muscle and bone pain are often present. Increased bone resorption is the presumed mechanism.[1] Of note: retinoids and not carotenoids are responsible for the characteristic clinical features of vitamin A toxicity.

This patient does not have the clinical features of vitamin A intoxication, and therefore this is the least likely cause.

Case continued: His PTH is low

On repeat testing, the patient's calcium level is 12.1 mg/dL; parathyroid hormone (PTH) level 4 pg/mL (normal 10–60 pg/mL); and phosphorus 4.4 mg/dL (normal 2.5–4.5 mg/dL).

ISSUES IN PTH MEASUREMENT

2 Regarding the measurement of PTH, which of these statements is *false*?

- ❑ The immunometric assays use two antibodies in a "sandwich" arrangement to detect the intact PTH peptide
- ❑ The PTH assay is useful even if a malignancy is present
- ❑ Biologically inactive PTH fragments are cleared more rapidly than the intact PTH peptide
- ❑ Ten percent to 20% of patients with primary hyperparathyroidism have serum PTH concentrations in the upper end of the normal range
- ❑ Plasma PTH concentrations are approximately 40% to 50% lower when measured by second-generation immunometric assays than by first-generation immunometric assays

PTH is difficult to measure, for technical reasons. Intact PTH is a peptide 84 amino acids long and is thus designated PTH (1–84). However, also present in the plasma, particularly in patients with renal failure, are biologically inactive carboxyl-terminal (C-terminal) fragments, ie, PTH molecules that are missing portions of their N-terminal ends. These are designated by the amino acids that remain, eg, PTH (7–84).

Immunometric assays for PTH use two antibodies in a "sandwich" to detect relatively longer peptides, presumed to be PTH (1–84).[2] However, first-generation immunometric PTH assays detect both PTH (1–84) and large N-terminally truncated PTH fragments such as PTH (7–84). In second-generation assays, antibodies attach to the N-terminal portion of the peptide and do not detect fragments without the terminal N region epitopes. Synthetic PTH peptides that are missing the N-terminal epitopes such as PTH (2–34), PTH (3–34), and PTH (7–84) will not cross-react with the antibodies used in the second-generation PTH assays. Hence, the second-generation assays detect only intact PTH and have a higher specificity.[2,3]

Plasma PTH concentrations are approximately 40% to 50% lower when measured by

second-generation immunometric assays than by first-generation immunometric assays, both in subjects with normal renal function and in patients with renal failure.[2,3] However, first-generation and second-generation immunometric assays correlate highly over a wide range of PTH concentrations in patients with end-stage renal disease and primary hyperparathyroidism.[2,3]

Intact PTH levels are usually elevated in primary hyperparathyroidism and with lithium treatment. However, 10% to 20% of patients with primary hyperparathyroidism have serum PTH concentrations in the upper end of the normal range.

A low or low normal PTH level is typical of non-PTH-related causes of hypercalcemia such as malignancy, excess vitamin D, high bone turnover, and renal failure.[1] However, patients with malignancy have an increased incidence of hyperparathyroidism, and so a PTH assay is useful even in patients with known malignancy.

The third statement is false (ie, it is the correct answer): clearance of the *intact hormone* from the blood is more rapid than the clearance of biologically inactive fragments, which consist of middle and C-terminal regions and are secreted by the parathyroid gland or are catabolic products.[4]

Case continued: Hepatic lesions are seen on CT

The patient's low PTH level raises a concern of malignancy, and further testing is ordered. The patient has a normal chest radiograph and prostate-specific antigen level. A colonoscopy is recommended to the patient. A computed tomography (CT) scan of the abdomen and pelvis is obtained because of his elevated alkaline phosphatase and palpable liver edge; it reveals numerous low-attenuation splenic and hepatic lesions with lymphadenopathy (FIGURE 1).

Comment. A serum gamma-glutamyl transferase measurement would have been useful in identifying the liver as the source of the elevated serum alkaline phosphatase concentration.

3 Which of the following statements about CT of the liver is true?

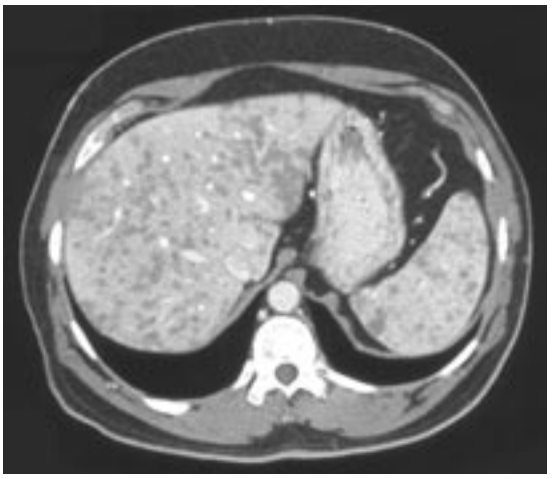

FIGURE 1. CT scan of patient's abdomen and pelvis.

- ❑ Helical CT is useful to characterize lesions and to detect vascular metastatic lesions
- ❑ The differential diagnosis of metastatic vascular hepatic lesions includes hepatocellular carcinoma, renal cell carcinoma, neuroendocrine islet tumor, breast cancer, melanoma, thyroid cancer, and sarcoma
- ❑ Helical CT has a sensitivity of about 90% in detecting nodules larger than 1 cm and about 55% for smaller nodules
- ❑ The differential diagnosis of the numerous subcentimeter lesions in the liver and spleen on this CT image includes sarcoidosis

The patient's low PTH raises the concern of malignancy

All the statements in the above question are true.

Conventional CT is less sensitive than ultrasonography in detecting hepatic lesions smaller than 1 or 2 cm and may miss lesions because of respiratory movements. Helical (spiral) CT allows the entire liver to be imaged during a single hold of the breath, thereby reducing artifacts.[5] A study of 21 patients with hepatic neoplasms (12 with primary hepatic lesions and 9 with metastases) found that spiral CT had a sensitivity of 91% for nodules bigger than 1 cm and 56% for nodules smaller than 1 cm.[6]

The findings of hypercalcemia, hepatic and splenic lesions, and lymphadenopathy on the CT scan make Hodgkin and non-Hodgkin lymphoma, sarcoidosis, and tuberculosis the leading differential diagnoses.

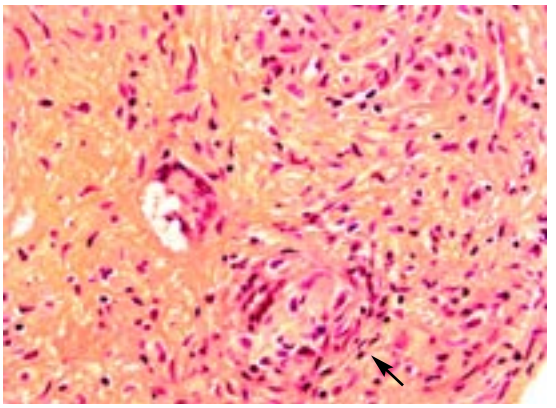

FIGURE 2. High-powered view of an epithelioid granuloma (arrow) with giant cells, histiocytes, and lymphocytes (hematoxylin and eosin, X 400).

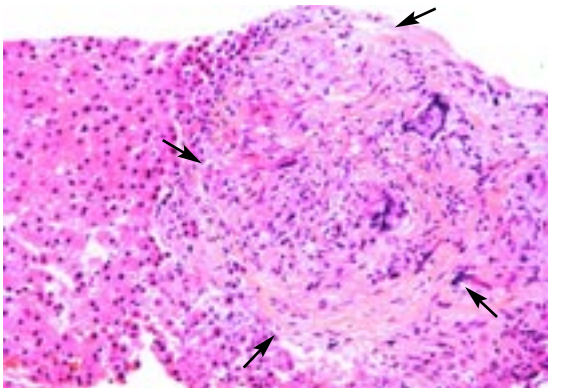

FIGURE 3. This image shows the classic finding of sarcoidosis, a compact and well-demarcated epithelioid granuloma (arrows) containing multinucleated giant cells and lymphocytes (hematoxylin and eosin, X 200).

Case continued: Sarcoidosis is diagnosed

The radiologist determines that the patient's CT findings "may represent leukemia or lymphoma." A CT-guided biopsy of the liver lesion is done and reveals nonnecrotizing granulomas without evidence of infection or malignancy on special staining (**FIGURES 2 AND 3**). Based on this information, a diagnosis of sarcoidosis is made.

Granulomas are found in up to 15% of patients on liver biopsy

Liver granulomas are common, often caused by infection

Granulomas are found in 3% to 15% of patients who undergo liver biopsy. In a retrospective review of 1,662 liver biopsies performed at the Glasgow Royal Infirmary in Scotland between 1991 and 2001, granulomas were found in 63 (3%) (**TABLE 2**). Forty-seven of the patients with granulomas were women, with a mean age of 42 years (range 17–81).[7] This series predated routine clinical testing for hepatitis C, currently an important cause of granulomas in the United Kingdom.

Systemic infections that cause granulomatous liver disease and fever include tuberculosis, infections related to acquired immunodeficiency syndrome (such as *Mycobacterium avium* complex), and cryptococcal infections. Fungal infections such as coccidioidomycosis, disseminated histoplasmosis, candidiasis, and blastomycosis also need to be considered. India-ink staining, acid-fast bacilli staining, and fungal and mycobacterial cultures are necessary in the relevant clinical settings when patients have typical pulmonary or extrapulmonary findings or both. Appropriate serologic testing for blastomycosis, coccidioidomycosis, and histoplasmosis and testing for cryptococcus antigen should be considered in relevant clinical scenarios. A purified protein derivative test should be performed.

Parasitic infections such as leishmaniasis and schistosomiasis should be considered in patients who live in or have visited areas in which such diseases are endemic. A case series from India documented 51 cases of granulomatous hepatitis among 1,234 liver biopsies over a 10-year period.[8] Tuberculosis was the most common cause, accounting for 55% of cases. Other causes included leprosy, sarcoidosis, histoplasmosis, brucellosis, amoebic liver abscess, lymphoma, and malignant granuloma. The cause remained unknown in 12%.

Clinically, these patients presented with fever and hepatosplenomegaly. Jaundice was uncommon. Many showed elevated alkaline phosphatase levels, anemia, and raised erythrocyte sedimentation rates. Granulomatous hepatitis of unknown cause with fever of unknown origin was seen in 6% of cases.

Our patient does not have a fever, constitutional symptoms, or pulmonary findings to suggest most of these diagnoses.

Granulomas are very common in sarcoidosis

Granulomatous liver involvement is seen in 40% to 70% of patients with sarcoidosis who undergo liver biopsies, although clinically sig-

nificant hepatic dysfunction is rare. Hepatomegaly or a cholestatic pattern of biochemical alterations, with minimal increases in aminotransferase levels, is seen in up to 30% of sarcoidosis patients.[9] The most common laboratory abnormality is a mildly elevated alkaline phosphatase.[10]

Most patients with sarcoidosis present with stage 1 disease (bilateral hilar lymphadenopathy) on chest radiography. Stage 0 (a normal chest radiograph with evidence of multisystem involvement, as in our patient), is seen in 8% to 10%.[11]

HOW DOES SARCOIDOSIS RAISE CALCIUM LEVELS?

4 Which of the following is true of the mechanisms of hypercalcemia in sarcoidosis?

- ❑ Calcitriol is produced from calcidiol by activated mononuclear cells (macrophages) in the lungs and lymph nodes independently of PTH
- ❑ PTHrP, the usual etiologic agent of humoral hypercalcemia of malignancy, may contribute to hypercalcemia in some patients with sarcoidosis
- ❑ Hypercalcemia and serum calcitriol elevations have been described in an anephric patient with sarcoidosis
- ❑ Calcidiol conversion to calcitriol can be demonstrated in vitro in alveolar macrophages or lymph node tissue of hypercalcemic patients with sarcoidosis

All of the above are true.

The relationship between sarcoidosis and hypercalcemia was first noted in 1939.[12] In the past, up to 50% of patients with sarcoidosis were reported to have hypercalciuria, and 10% to 20% had hypercalcemia that was due to extrarenal synthesis of 1,25-dihydroxyvitamin D_3.[13]

However, the more recent Case Control Etiologic Study of Sarcoidosis (ACCESS) found a lower prevalence of hypercalcemia (3.7%) in the 736 patients included in the study.[14] The prevalence was higher in Caucasians than in African Americans, in men than in women, and in patients older than 40 years than in younger.[14] (Recall that our patient is a 56-year-old man from Guyana, a South American country where ancestries are mixed from Africa, Asia, Europe, and North and South America. He appears to be of mixed black and Asian races.)

TABLE 2

Causes of liver granulomas*

CAUSE	PREVALENCE (%)
Primary biliary cirrhosis	23.8
Sarcoidosis	11.1
Idiopathic	11.1
Drug-induced	9.5
Hepatitis C	9.5
Primary biliary cirrhosis/autoimmune hepatitis overlap	6.3
Hodgkin lymphoma	6.3
Autoimmune hepatitis	4.8
Tuberculosis	4.8
Resolving biliary obstruction	3.2
Other single miscellaneous causes	9.5

*In a 10-year series of 1,662 liver biopsies in the United Kingdom.

GAYA DR, THORBURN D, OIEN KA, MORRIS AJ, STANLEY AJ. HEPATIC GRANULOMAS: A 10 YEAR SINGLE CENTRE EXPERIENCE. J CLIN PATHOL 2003; 56:850–853. REPRODUCED WITH PERMISSION FROM THE BMJ PUBLISHING GROUP

Risk factors for the development of hypercalcemia in patients with sarcoidosis include renal insufficiency, increased dietary vitamin D, and increased sunlight exposure.[11] Increased bowel absorption caused by a high calcitriol level is the main abnormality. Increased bone resorption caused by calcitriol is a less important cause.

Comment. Our patient has an elevated creatinine level (1.5 mg/dL) with a blood urea nitrogen (BUN) level of 19 mg/dL and a BUN/creatinine ratio of 13. The elevated creatinine is likely due to reversible renal tubular defects (seen in hypercalcemia) causing reduced tubular secretion of creatinine; the interference with renal tubular concentrating function may lead to volume depletion, but our patient is not volume-depleted. In addition, direct hemodynamic effects may cause afferent arteriolar vasoconstriction leading to acute renal failure.[13]

His abdominal CT scan shows no evidence of obstructive uropathy, chronic parenchymal disease, or nephrocalcinosis. Renal ultrasonography would have been appropriate to evaluate the renal parenchyma.

Hypercalciuria with or without hypercalcemia may cause nephrocalcinosis and renal failure, but significant glomerular, tubular, or arterial involvement is rare in sarcoidosis.[9]

TREATMENT

5 Which of the following is *not* a treatment option for hypercalcemia in sarcoidosis?

- ❑ Low-dose glucocorticoid therapy
- ❑ Ketoconazole
- ❑ Hydroxychloroquine
- ❑ Bisphosphonates
- ❑ Hydrochlorothiazide

After the diagnosis of sarcoidosis with hypercalcemia is established, further workup may include bone densitometry, 24-hour urine calcium measurement, and a screen for renal calculi.[13]

Standard treatment for symptomatic hypercalcemia or a calcium value greater than 12 mg/dL involves **low-dose glucocorticoids** (eg, prednisone 10–30 mg/day). The serum calcium level usually begins to fall within 48 hours of starting prednisone, but a full response may take 7 to 10 days.

Ketoconazole or **hydroxychloroquine** is an alternative if corticosteroids are contraindicated.[13,15,16] Ketoconazole, an imidazole antifungal agent, inhibits macrophage 1-alpha-hydroxylation of 25-hydroxyvitamin D_3. It has been tried with some success in a handful of patients with hypercalcemic sarcoidosis in view of previous successes in treating paraneoplastic hypercalcemia.

Biphosphonates such as pamidronate can be useful if prednisone is ineffective.

Reduce calcium and vitamin D. Intestinal calcium absorption and calcitriol synthesis can be reduced by reducing calcium and oxalate intake, stopping all vitamin D supplements, and avoiding sun exposure.

Of note: all perimenopausal women with sarcoidosis and patients on steroids need to be educated and screened appropriately for osteoporosis. Treatment with calcium supplements, vitamin D, and antiresorptive agents such as alendronate and risedronate needs to be individualized.

Hydrochlorothiazide is contraindicated in patients with sarcoidosis with hypercalcemia,[17] although it reduces calcium excretion and is useful in patients with recurrent calcium stones.

Case resolved

When questioned about his dietary habits, the patient reports that he drinks three large glasses of milk a day and has recently started taking his wife's calcium and vitamin D supplements. He is instructed to decrease his consumption of calcium and vitamin D. After this intervention, his calcium level declines to 10.4 mg/dL and remains normal on follow-up.

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