May 2016 Critical Care Case of the Month

Layth Al-Jashaami, MD
Yousef Usta, MD
Negin N. Blattman, MD
Rakesh Nanda, MD

Phoenix VA Health Care System
650 E Indian School Road
Phoenix, Arizona, 85012 USA

History of Present Illness

A 50-year-old African American woman presented with weakness, altered mental status and constipation of 12 days duration. She was complaining of abdominal distension with diffuse pain and bloating. She denied melena, hematochezia or hematemesis. She had a history weight loss, anorexia and fatigue which had evolved over the past few months leading to recent severe weakness and inability to get out of bed.

Past Medical History, Social History and Family History

Her past medical history included HIV infection with AIDS and noncompliance with her antiretroviral medications. Her most recent CD4 count was <20 cells/uL and viral load of 554,483 copies/mL.

Physical Examination

Vital signs: Blood pressure, 120/80 mmHg, heart rate, 105/min, temperature, 98.6° and respiratory rate, 20/min.
General: Physical examination showed a lethargic female who was poorly responsive to questioning.
Abdomen: Distended, tympanic abdomen with hypoactive bowel sounds and diffuse tenderness.

Radiography

Plain x-ray examination of the abdomen on admission is shown in Figure 1.

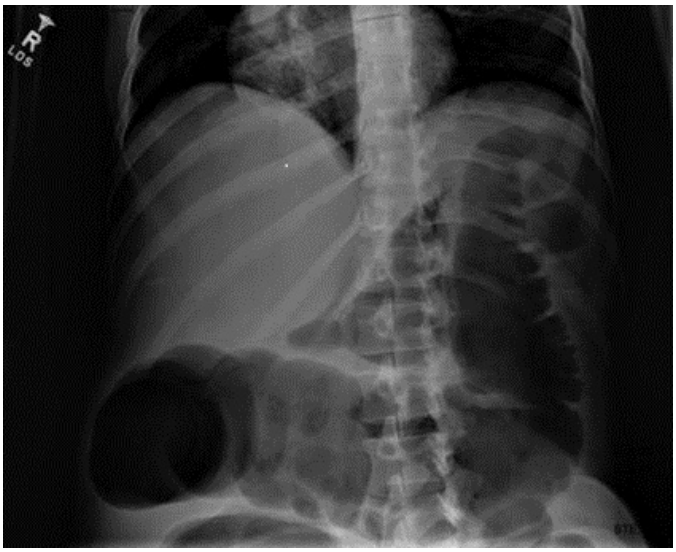

Figure 1. Admission x-ray of the abdomen.

Which of the following are ***possible causes*** of the patient's complaints, physical findings and abdominal x-ray findings?

1. Electrolyte disturbances
2. Use of anticholinergic drugs
3. Use of narcotics
4. 1 and 3
5. All of the above

Correct!
5. All of the above

The abdominal x-ray shows a large amount of stool in the retrosigmoid region with a moderate amount of stool in the right colon and gaseous distention of the transverse colon. This combined with her complaints and physical findings suggests intestinal obstruction or psudeo-obstruction. The later occurs when findings are suggestive of obstruction in the absence of any demonstrable mechanical obstruction and is also known as Ogilvie Syndrome. All of the listed causes may cause intestinal pseudo-obstruction although a transient postoperative ileus is the most common cause (1).

Certainly drug abuse with sharing of needles has been a common cause of HIV+ and AIDS. Anticholinergic abuse might also case pseudo-obstruction although usually not in this clinical situation.

Laboratory evaluation was performed to examined for electrolyte disturbances and the serum calcium was found to be markedly elevated at 15.1 mg/dL (normal 8.6-10.4 mg/dL. .

The mechanism of how hypercalcemia causes significant constipation is not well understood, but may be related to decreased intestinal smooth muscle tone and associated with abnormal autonomic nerve function (2).

Which of the following ***laboratory tests should be ordered*** to determine the cause of her hypercalcemia?

1. 1,25-dihydroxy vitamin D3
2. Alkaline phosphatase
3. Parathyroid hormone
4. 1 and 3
5. All of the above

Correct!
5. All of the above

The causes of hypercalcemia can be largely divided into two categories: excessive release of calcium from bones or increased absorption from the gastrointestinal tract. Pertinent findings of her laboratory evaluation of hypercalcemia are shown in Table 1.

Table 1. Pertinent laboratory tests.

Laboratory test	Serum Level	Normal Values
Calcium	15.1	8.6-10.4 mg/dL
Ionized Calcium	1.74	1.12-1.32 mmol/L
Albumin	3.2	3.5-5.1 gm/dL
Parathyroid Hormone	23	10-65 pmol/L
Parathyroid hormone-related protein	27	14-27 pg/ML
1,25-dihydroxy vitamin D_3	92	18-72 pg/mL
25-hydroxyvitamin D_3	60.4	30-60 ng/mL
Alkaline phosphatase	262	30-120U/L

Which of the ***following mechanism(s)*** are most consistent with the cause of the hypercalcemia ***in our patient***?

1. Overproduction of 1,25-dihydroxy vitamin D_3
2. Overproduction of parathyroid hormone due to primary hyperparathyroidism
3. Overproduction of parathyroid hormone-related protein
4. 1 and 3
5. All of the above

Correct!
4. 1 and 3

The low normal parathyroid hormone level would seem to exclude primary hyperparathyroidism in which a tumor of the parathyroid gland produces excessive amount of parathyroid hormone (3). However, both the 1,25-dihydroxy vitamin D_3 and parathyroid hormone-related protein are elevated or at the upper limit of normal. The elevated alkaline phosphatase suggests either bone or liver lesions. However, her other liver enzymes were normal.

Which of the following should be ***performed next***?

1. Bone scan
2. Hemodialysis
3. IV hydration
4. 1 and 3
5. All of the above

Correct!
4. 1 and 3

Aggressive hydration is the treatment of choice for hypercalcemia (3). Bisphosphonates may also be given. In our opinion, hemodialysis is overly aggressive and should be reserved for emergency situations or those failing hydration and bisphosphonates. Normal saline was administered intravenously. She was also given a bisphosphonate, pamidronic acid, 60 mg IV once a day.

A bone scan showed diffuse miliary lesions in the pelvis, elbows, right wrist, thumb, knees, distal right tibia, ankles and feet (Figure 2).

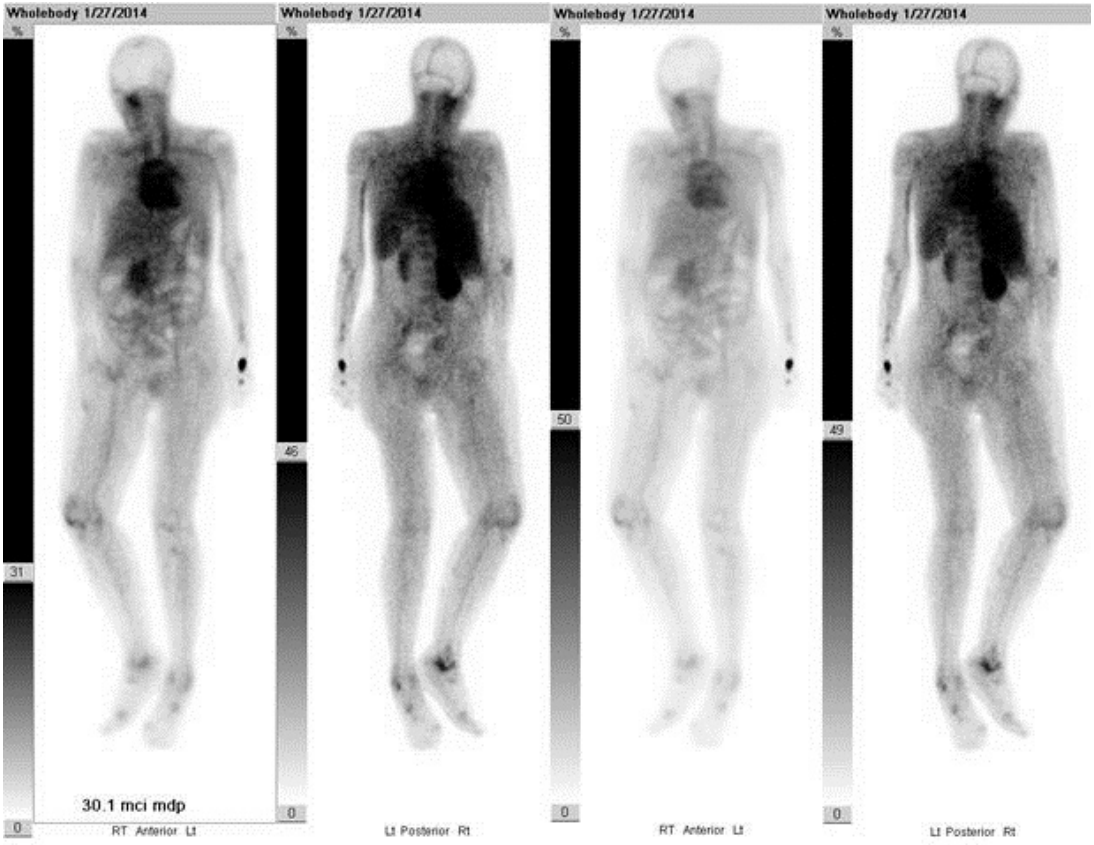

Figure 2. Bone scan showing diffuse uptake of radiotracer in multiple bones.

Which of the following ***<u>should be done next</u>***?

1. Bone biopsy
2. Coccidioidomycosis serology
3. Serum angiotensin converting enzyme level (ACE)
4. 1 and 3
5. All of the above

Correct!
2. Coccidioidomycosis serology

A coccidioidomycosis serology was markedly positive making a presumptive diagnosis of Valley Fever. A bone biopsy is not necessarily wrong but given a positive coccidioidomycosis serology and a compatible clinical situation is probably not necessary. Serum ACE is often elevated in sarcoidosis but it is unclear how this would have helped in this situation. The patient was begun on fluconazole in addition to her hydration and bisphosphonate therapy. Her serum calcium rapidly returned to the normal range (Figure 3).

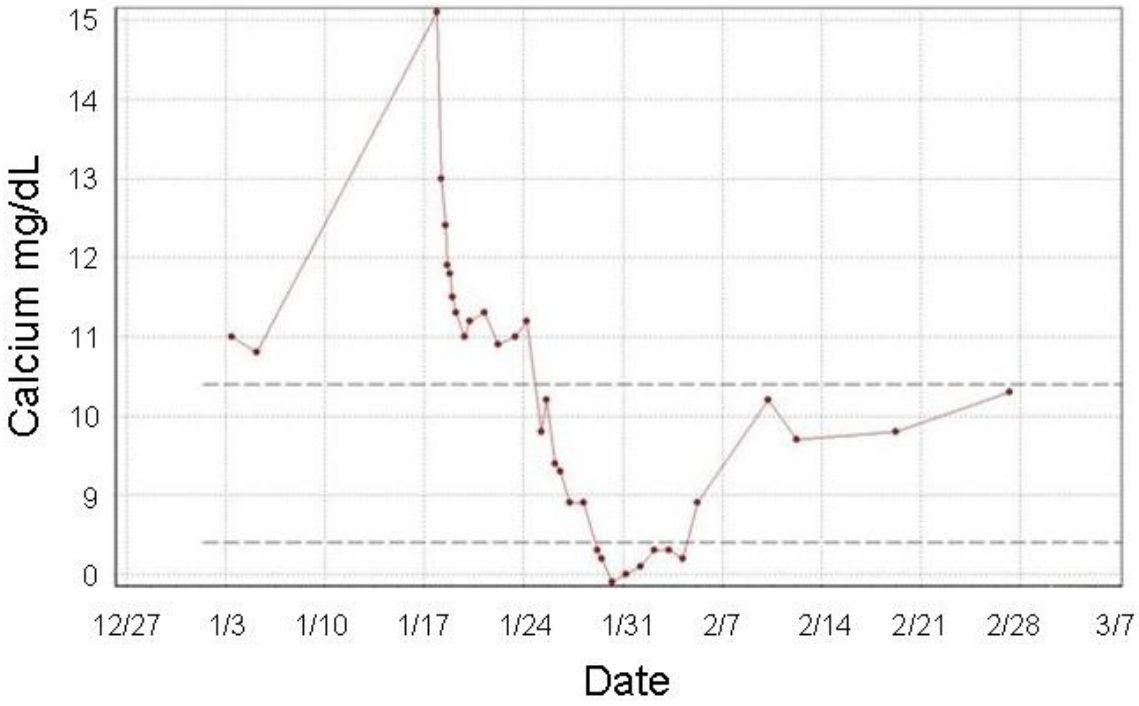

Figure 3. Calcium levels during admission. The two normal levels are from previous testing done prior to admission.

Clinically the patient's pseudo-obstruction resolved at a calcium level 8.3 mg/dL and she was eventually discharged. After discharge her calcium levels gradually rose again, so she given chronic bisphosphonates (IV) therapy every 3 months and her calcium levels remained controlled.

Reports of hypercalcemia have been described associated with sarcoidosis, tuberculosis and other granulomatous disorders (4-6). Coccidioidomycosis is a an endemic granulomatous fungal infection found in southwestern United States and known to cause hypercalcemia when the infection is disseminated and involves bone (7-9).

The mechanisms for a granulomatous disease to cause hypercalcemia are not well defined. The overproduction of 1, 25-dihydroxy vitamin D, does occur in sarcoidosis and has been generalized to other granulomatous diseases (8). Calcitriol mediated bone resorption and the production of parathyroid related protein (PTHrP) may also play a role. PTHrP is expressed in most granulomatous lesions but does not necessarily cause hypercalcemia. Fierer, *et al.* (10) hypothesized that the number of fungal lesions that make PTHrP and the amount produced by each lesion likely plays a role in causing hypercalcemia in coccidioidomycosis. Nearly all the reported cases of infection associated hypercalcemia are the result of disseminated infections. Therefore, an important variable causing this form of hypercalcemia is the number of granulomas able to produce measurable serum levels of PTHrP and this was documented in our patient.

It has been recommended that patients with hypercalcemia due to disseminated coccidioidomycosis should be treated with antifungal therapy and hydration (10,11). Patients with very high levels of calcium such as 15.1 mg/dL may benefit from intravenous hydration and bisphosphonates (11). Symptomatic hypercalcemia causing Ogilvie Syndrome needs to be corrected aggressively because the condition can be very serious and the mortality rate as high as 30% (11).

References

1. Di Lorenzo C. Pseudo-obstruction: current approaches. Gastroenterology. 1999 Apr;116(4):980-7. [CrossRef] [PubMed]
2. Gardner EC Jr, Hersh T. Primary hyperparathyroidism and the gastrointestinal tract. South Med J. 1981 Feb;74(2):197-9. [CrossRef] [PubMed]
3. Agraharkar M. Hypercalcemia. Medscape. June 23. 2015. Available at: http://emedicine.medscape.com/article/240681-overview (accessed 4/25/16).
4. Fuss M, Pepersack T, Gillet C, Karmali R, Corvilain J. Calcium and vitamin D metabolism in granulomatous diseases. Clin Rheumatol. 1992 Mar;11(1):28-36. [CrossRef] [PubMed]
5. Deniz O, Tozkoparan E, Yonem A, et al. Low parathormone levels and hypercalcaemia in patients with pulmonary tuberculosis: relation to radiological extent of disease and tuberculin skin test. Int J Tuberc Lung Dis. 2005 Mar;9(3):317-21. [PubMed]
6. Shrayyef MZ, DePapp Z, Cave WT, Wittlin SD. Hypercalcemia in two patients with sarcoidosis and Mycobacterium avium intracellulare not mediated by elevated vitamin D metabolites. Am J Med Sci. 2011 Oct;342(4):336-40. [CrossRef] [PubMed]
7. Lee JC, Catanzaro A, Parthemore JG, Roach B, Deftos LJ. Hypercalcemia in disseminated coccidioidomycosis. N Engl J Med. 1977 Aug 25;297(8):431-3. [CrossRef] [PubMed]

8. Westphal SA. Disseminated coccidioidomycosis associated with hypercalcemia. Mayo Clin Proc. 1998 Sep;73(9):893-4. [CrossRef] [PubMed]
9. Caldwell JW, Arsura EL, Kilgore WB, Reddy CM, Johnson RH. Hypercalcemia in patients with disseminated coccidioidomycosis. Am J Med Sci. 2004 Jan;327(1):15-8. [CrossRef] [PubMed]
10. Fierer J, Burton DW, Haghighi P, Deftos LJ. Hypercalcemia in disseminated coccidioidomycosis: expression of parathyroid hormone-related peptide is characteristic of granulomatous inflammation. Clin Infect Dis. 2012 Oct;55(7):e61-6. [CrossRef] [PubMed]
11. Legrand SB. Modern management of malignant hypercalcemia. Am J Hosp Palliat Care. 2011 Nov;28(7):515-7. [CrossRef] [PubMed]