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.
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

Figure 1. Admission x-ray of the abdomen.
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 pseudo-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 cause 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.

<table>
<thead>
<tr>
<th>Laboratory test</th>
<th>Serum Level</th>
<th>Normal Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>15.1</td>
<td>8.6-10.4 mg/dL</td>
</tr>
<tr>
<td>Ionized Calcium</td>
<td>1.74</td>
<td>1.12-1.32 mmol/L</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.2</td>
<td>3.5-5.1 gm/dL</td>
</tr>
<tr>
<td>Parathyroid Hormone</td>
<td>23</td>
<td>10-65 pmol/L</td>
</tr>
<tr>
<td>Parathyroid hormone-related protein</td>
<td>27</td>
<td>14-27 pg/mL</td>
</tr>
<tr>
<td>1,25-dihydroxy vitamin D₃</td>
<td>92</td>
<td>18-72 pg/mL</td>
</tr>
<tr>
<td>25-hydroxyvitamin D₃</td>
<td>60.4</td>
<td>30-60 ng/mL</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>262</td>
<td>30-120U/L</td>
</tr>
</tbody>
</table>

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 D₃
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
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 D₃ 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 should be done next?

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.](image)

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 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