We recommend monitoring of serum calcium after initiation of antifungal treatment, especially in patients with underlying hypercalcemia. More studies are needed to understand the pathophysiology.

INTRODUCTION

Histoplasma capsulatum var. duboisii and Histoplasma capsulatum var. capsulatum are the two pathogenic varieties that cause histoplasmosis in humans. The first exists only in Africa whereas the second (referred hereafter as $H. \text{capsulatum}$) exists mainly in North America and Central America. In the United States, $H. \text{capsulatum}$ is endemic in the Mississippi and Ohio River valleys [1].

A 61-year-old Caucasian male from Kansas, USA, presented with shortness of breath, cough, weight loss, but no fever or hemoptysis. His physical exam was unremarkable except for decreased air entry on both lung fields, and axillary and inguinal lymphadenopathies.

Computed tomography of the chest showed bilateral cavitory lung lesions, biopsy of which showed non-caseating granulomas, and tissue culture showing $\text{Histoplasma capsulatum}$. Itraconazole was started. One month later, patient presented with transient acute renal failure and worsening hypercalcemia. His work-up showed a non-PTH mediated hypercalcemia, with a normal PTH-rP, and low calcifediol, but high normal calcitriol level. Hypercalcemia secondary to histoplasmosis was reported in six cases, none of which worsened after antifungal treatment. Several mechanisms have been elucidated.

CONCLUSION: We recommend monitoring of serum calcium after initiation of antifungal treatment, especially in patients with underlying hypercalcemia. More studies are needed to understand the pathophysiology.

RÉSUMÉ: L’histoplasmose peut induire une hypercalcémie, complication connue mais raraissime de cette maladie granulomateuse. Nous présentons un cas d’histoplasmose chronique disséminée compliquée par une hypercalcémie, celle-ci s’étant aggravée temporairement suite à l’initiation du traitement antifongique.

Présentation du cas: Un homme âgé de 61 ans s’est présenté pour dyspnée, toux, perte de poids. A noter l’absence de fièvre et d’hémoptysie. L’examen physique était dans les limites de la normale à l’exception d’une diminution de l’entrée d’air bilatérale, et de la présence d’adénopathies dans les régions axillaires et inguinales. La tomodensitométrie du thorax a montré l’existence de lésions cavitaires pulmonaires bilatérales. La culture des tissus a révélé l’$\text{Histoplasma capsulatum}$. Le patient a été traité avec l’itraconazole. Un mois plus tard ce dernier se présente avec une insuffisance rénale aiguë transitoire et une hypercalcémie progressive. Le bilan effectué révèle une hypercalcémie non liée à la PTH, avec une PTH-rP normale, un bas taux de calcifediol et un taux de calcitriol à la limite supérieure de la normale. L’hypercalcémie secondaire à l’histoplasmose a été rapportée dans six cas, aucun n’a éclucidé une aggravation de l’hypercalcémie après initiation du traitement antifongique. Plusieurs mécanismes ont été impliqués.

CONCLUSION: Nous recommandons de surveiller étroitement le dosage de la calcémie suite à l’initiation de tout traitement antifongique, en particulier chez les patients ayant une hypercalcémie sous-jacente. Des études poussées s’avèrent nécessaires pour expliciter la physiopathologie.

We present a case of hypercalcemia secondary to chronic disseminated histoplasmosis in a 61-year-old immunocompetent gentleman. Hypercalcemia is a rare complication of histoplasmosis reported only in six cases [2-7].

CASE PRESENTATION

A 61-year-old Caucasian male from Kansas, USA, presented with shortness of breath on minimal effort and dry cough associated with fatigue, night sweats, poor appetite, and a 15-pound weight loss over the prior two months. The review of systems revealed the presence of constipa-
tion, nausea, and nocturia. He denied any fever, chest pain, hemoptysis, or hematuria. His medical history was relevant for hypertension and alcoholic liver disease. His medications were limited to metoprolol for blood pressure and loratadine for allergies. He denied any supplement use. He smoked two packs of cigarette per day for the past 40 years and drank alcohol on daily basis. He worked on a farm for 20 years, but quit working five years ago. He denies any other chronic exposures.

On presentation, his vital signs were within normal limits. His pertinent physical exam findings were decreased air entry in both lung fields and enlarged lymph nodes in the right axilla and the groin. QuantiFERON®-TB Gold and HIV screening tests, blood culture, and sputum culture, were negative. His creatinine was 1.28 mg/dl (an increase from his baseline of 0.7 mg/dl). His labs included calcium of 10.9 mg/dl, albumin of 2.8 g/dl, white blood cells of 3.3 K/mm³, platelets of 140 K/mm³, and hemoglobin of 12.7 g/dl.

The workup for his hypercalcemia showed a low parathyroid hormone (PTH) of 9.9 pg/ml, a low calcifediol (25-hydroxycholecalciferol, or 25-hydroxyvitamin D) of 18 ng/ml, and a high angiotensin-converting enzyme (ACE) level of 309 U/L. Parathyroid hormone-related peptide and 24-hour urinary calcium were within normal limits. Serum protein electrophoresis (SPEP) and urine protein electrophoresis (UPEP) were normal. Vitamin A, TSH and AM cortisol levels (13.3 mcg/dl) were normal. The workup for the acute renal failure showed a urine sodium less than 20 mEq and the fraction excretion of sodium was 0.56%. The renal ultrasound was normal. The pancytopenia was initially thought to be from alcohol use.

A computed tomography (CT) scan of the chest showed cavitary lung nodules (Figure 1) and CT guided lung biopsy showed multiple non-caseating granulomas, with the presence of multinucleated giant cells. Extensive workup including CT of the abdomen and pelvis and skeletal survey were negative.

Later, the lung tissue culture came back positive for *H. capsulatum*. Itraconazole was initiated. One month later he presented again with a creatinine of 2.35 mg/dl and a calcium level of 13.4 mg/dl. His albumin was 3.2 g/dl. At this time, he had a low normal PTH level of 16.9 pg/ml and a normal parathyroid hormone-related peptide (PTH-rP). His calcifediol level (25-hydroxycholecalciferol, or 25-hydroxyvitamin D) was low at 24 ng/ml and his calcitriol level was high normal at 53 pg/ml. Intravenous hydration and subcutaneous calcitonin were initiated as an inpatient, with quick resolution of his kidney injury. His hypercalcemia persisted, requiring intravenous pamidronate on two separate occasions.

Six months after his admission, the patient was still on itraconazole 200 mg daily and remained asymptomatic with normal calcium level and renal function.

DISCUSSION

*H. capsulatum* causes a large spectrum of diseases, ranging from asymptomatic or very limited disease to serious infection [1]. This spectrum includes:

- **Acute pulmonary histoplasmosis**, a self-limited illness characterized by dry cough, fever, weakness, and chest discomfort or even acute respiratory distress syndrome (ARDS) in immunosuppressed hosts [8];

- **Chronic cavitary pulmonary histoplasmosis** occurs in patients with preexisting pulmonary disease and is characterized by the presence of cavitary lung lesions causing dyspnea, cough, and hemoptysis with fever and weight loss;

- **Disseminated histoplasmosis** characterized by fever, weight loss, hepatosplenomegaly, and lymphadenopathy. The acute form occurs mainly in immunosuppressed subjects, whereas chronic disseminated histoplasmosis occurs mostly in immunocompetent older adults.

Our patient’s age, immunocompetent status, clinical presentation, physical exam findings (lymphadenopathy), laboratory findings (pancytopenia, hypercalcemia) and eventually the pathology findings (non-caseating granulomas and positive *H. capsulatum* tissue culture) all con-

![Figure 1. CT scan of the chest.](image-url)
firmed the diagnosis of chronic disseminated histoplasmosis. The low PTH, normal phosphorus, and normal parathyroid hormone-related peptide ruled out PTH mediated hypercalcemia. In this setting, the inappropriately high normal calcitriol along with a low calcifediol can only be explained by an extra-renal production of calcitriol. Also, given the patient's high calcium, we would expect his calcitriol level to be suppressed. Hypercalcemia is associated with many granulomatous diseases [9], including histoplasmosis [2-7]. The most accepted pathophysiology is increased macrophagic 1\(\alpha\)-hydroxylase activity in the granulomatous lesions leading to overproduction of active calcitriol and eventually hypercalcemia [10]. Based on these data, we concluded that the hypercalcemia in our patient was due to the chronic disseminated histoplasmosis.

Hypercalcemia secondary to histoplasmosis was reported in six cases [2-7]. Table I compares the known reported cases. In all these cases, hypercalcemia was part of the initial presentation. In our patient, however, hypercalcemia worsened after the initiation of the antifungal therapy, suggesting a clinical scenario similar to immune reconstitution inflammatory syndrome (IRIS) in acquired immunodeficiency syndrome (AIDS) patients.

Hypercalcemia secondary to granulomatous diseases associated IRIS in AIDS patients were reported in six cases [11-12]. In these cases, the restoration of the host immune system results in activation of the macrophages in granulomatous tissue that leads to calcitriol production and hypercalcemia [10].

The treatment of hypercalcemia in granulomatous diseases is based mainly on reducing calcitriol production by activated macrophages in granulomatous tissue. Low dose prednisone could be adequate [13]. In resistant cases, bisphosphonate can be used [14]. More studies are needed to evaluate the use of ketoconazole in histoplasmosis-related hypercalcemia [10]. This effect is absent in itraconazole [10], however, the IDSA guidelines recommend itraconazole for mild-moderate chronic disseminated histoplasmosis. Other components of treatment include reducing calcium, oxalate, and vitamin D intake. In our patient, a steroid was not used because of the infection, nevertheless pamidronate was successful in controlling hypercalcemia.

### Table I

<table>
<thead>
<tr>
<th>Location/System Involved</th>
<th>Ca Level (mg/dl)</th>
<th>Albumin (g/dl)</th>
<th>PTH (pg/ml)</th>
<th>Calcifediol (ng/ml)</th>
<th>Calcitriol (ng/ml)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walker et al. [2]</td>
<td>12.7 mg/dl</td>
<td>2.5 g/dl</td>
<td>59 pg/ml</td>
<td>n/a</td>
<td>n/a</td>
<td>Patient died</td>
</tr>
<tr>
<td>Murray et al. [3]</td>
<td>13.8 mg/dl</td>
<td>2.1 g/dl</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>Patient died</td>
</tr>
<tr>
<td>Steele et al. [4]</td>
<td>12.6 mg/dl</td>
<td>2.1 g/dl</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Clinical improvement and normalized Ca</td>
</tr>
<tr>
<td>Liu et al. [5]</td>
<td>13.2 mg/dl</td>
<td>1.8 g/dl</td>
<td>&lt; 1 pg/ml</td>
<td>n/a</td>
<td>n/a</td>
<td>Patient died</td>
</tr>
<tr>
<td>Liang et al. [6]</td>
<td>13.8 mg/dl</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>18 ng/ml</td>
<td>Clinical improvement and normalized Ca</td>
</tr>
<tr>
<td>Kamili et al. [7]</td>
<td>12.8 mg/dl</td>
<td>8 pg/ml</td>
<td>4 ng/ml</td>
<td>Normal</td>
<td>97 pg/ml</td>
<td>Clinical improvement and normalized Ca</td>
</tr>
<tr>
<td>Our case - Initial</td>
<td>10.9 mg/dl</td>
<td>2.8 g/dl</td>
<td>9.9 pg/ml</td>
<td>18 ng/ml</td>
<td>n/a</td>
<td>Transient increase in Ca followed by clinical improvement and normalized Ca</td>
</tr>
<tr>
<td>After starting itraconazole</td>
<td>13.4 mg/dl</td>
<td>3.2 g/dl</td>
<td>16.9 pg/ml</td>
<td>24 ng/ml</td>
<td>53 pg/ml</td>
<td>Transient increase in Ca followed by clinical improvement and normalized Ca</td>
</tr>
</tbody>
</table>

n/a: not available  
Ca: calcium  
PTH: parathyroid hormone  
a: converted from 3.3 mmol/L  
b: 25 OH Vitamin D2 level  
c: drawn a few weeks prior
ACKNOWLEDGMENTS

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REFERENCES