Vitamin D-Mediated Hypercalcemia as the Initial Manifestation of Pulmonary Cryptococcosis in an HIV-uninfected Patient

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Abstract

Hypercalcemia has been described in variety of granulomatous diseases and fungal infections. However, hypercalcemia in pulmonary cryptococcosis is rarely disclosed. We report a 57-year-old HIV-uninfected woman with diabetes, who initially presented with altered mental status, severe hypercalcemia with increased serum 1,25-dihydroxyvitamin D [1,25(OH)₂D] concentration and suppressed parathyroid hormone. Pulmonary cryptococcosis was diagnosed as the cause of hypercalcemia. Successful treatment resulted in the resolution of hypercalcemia and decrease of the serum 1,25(OH)₂D concentration to within the normal range. In summary, although HIV infection is a major risk factor for cryptococcosis, vitamin D-mediated hypercalcemia could be the initial presentation of pulmonary cryptococcosis in HIV-negative patients.

Key words: cryptococcosis, hypercalcemia, vitamin D


Introduction

Hypercalcemia is not a rare problem in medical practice. The most common causes of hypercalcemia are primary hyperparathyroidism and malignancy, accounting for greater than 90 percent of cases (1). A variety of granulomatous diseases and fungal infections cause hypercalcemia as well. Pulmonary cryptococcosis can be manifested by asymptomatic, fever, pneumonitis, hemoptysis, and pulmonary mass (2). However, initial presentation as hypercalcemia and altered consciousness is extremely rare in pulmonary cryptococcosis.

Here, we describe a woman with presentation of confused mental status, caused by marked hypercalcemia, suppressed parathyroid hormone (PTH) and increased serum 1,25-dihydroxyvitamin D [1,25(OH)₂D] levels. She was finally diagnosed with pulmonary cryptococcosis. Successful treatment lead to the resolution of hypercalcemia and decrease of the 1,25(OH)₂D concentration to within the normal range.

Case Report

A 57-year-old woman, presenting with confused mental status for one week, was brought to our hospital in mid-February, 2010. For several years she was treated for diabetes mellitus, hypertension and gout. At presentation, her blood pressure was 152/78 mmHg, body temperature was 37.6°C, pulse rate was 114/min and respiratory rate was 14/min. Confusion, disorientation and incoherent speech without focal neurologic deficits were discovered on neurologic examination. No pulmonary symptoms, including cough, dyspnea and hemoptysis, were noted. Other physical examination was unremarkable. Non-contrast brain computerized tomography (CT) showed mild encephalomalacia in the left frontal lobe.

The laboratory data revealed white blood cell count 10,200/μL, hemoglobin 10.1 g/dL and platelet count 367,000/μL. Surprisingly, the biochemical blood tests yielded marked hypercalcemia with a total calcium of 15.4...
mg/dL, ionized calcium of 7.45 mg/dL and acute kidney injury with blood urea nitrogen of 29.8 mg/dL and creatinine of 3.24 mg/dL, phosphate 2.3 mg/dL and glucose 112 mg/dL. The spot urine calcium-to-creatinine ratio was 0.30 mg/mg. In addition, serum parathyroid hormone (PTH) level was 6.53 pg/mL (normal range, 11 to 62 pg/mL), alkaline phosphatase was 99 IU/L, 25-hydroxyvitamin D was 36 ng/mL (normal range, 5.3 to 27.1 ng/mL) and 1,25(OH)2D was 109 pg/mL (normal range, 15.9 to 55.6 pg/mL). However, parathyroid hormone-related protein (PTHrP) measurement was not available at our hospital. Thyroid function tests were normal.

She was managed with intravenous fluid supplement, pamidronate 90 mg and several subcutaneous injections of calcitonin for hypercalcemia. She regained oriented mental status, baseline renal function, and normal ionized calcium level in one week (Fig. 1). Based on the findings of hypercalcemia with suppressed PTH and an inappropriately high 1,25(OH)2D level, we started to search for occult malignancy and granulomatous disease. Nasopharyngeal fiberscope, gastrointestinal endoscopy, and Pap smear were negative for malignancy. Her chest radiograph demonstrated small nodules in the right lung, and CT of the chest showed granulomas with air crescent sign in the right middle lobe (Fig. 2) and a left thyroid mass. Sputum and bronchoscopic studies both revealed negativity for acid-fast bacilli, bacteria and fungi. Aspiration findings of left thyroid mass showed papillary thyroid carcinoma. Iodine-131 thyroid whole body scan showed no evidence of metastasis, as well as no bony metastasis on bone scan.

Her serum cryptococcal antigen was positive at a level of 1:1 and HIV test was negative. Accordingly, pulmonary cryptococcosis was suspected. Subsequent lumbar puncture for cerebrospinal fluid analysis yielded no pleocytosis and negative results for India ink, cryptococcal antigen, and fungus culture. Thus, we excluded central nervous system (CNS) involvement of cryptococcosis. Therefore, she underwent video-assisted thoracoscopic lobectomy of the right middle lobe. Pathology and tissue culture confirmed Cryptococcus neoformans infection (Fig. 3).

As a result, she received antifungal therapy of fluconazole 400 mg daily for 8 weeks. Hypercalcemia was resolved with ionized calcium 4.97 mg/dL and PTH 9.78 pg/mL. Serum cryptococcal antigen turned negative and the serum 1,25(OH)2D level of 43.2 pg/mL was normal. She had normal ionized calcium during follow-up and underwent total thyroidectomy 5 months after completion of fluconazole treatment.

**Discussion**

Cryptococcosis is more common in immunocompromised patients, such as those with impaired cell-mediated immunity, HIV infection, solid organ transplantation, hematologic malignancies, and those on chronic corticosteroids or immunosuppressive therapy (2). Pulmonary cryptococcosis can
be manifested by asymptomatic, cough, hemoptysis, pneumonitis, and lung mass. Initial presentation as hypercalcemia and altered mental status is infrequently reported, even in HIV-positive or immunocompromised patients. To our best knowledge, only 3 cases were reported to have hypercalcemia associated with cryptococcosis; two cases with HIV infection were reported by Spindel et al. (3) and Ali et al. (4) and another one with end-stage renal disease was reported by Wang et al. (5). The present case is the first case in an HIV-uninfected and non-uremic patient.

Hypercalcemia with suppressed PTH can be caused by malignancies, varieties of granulomatous diseases and fungal infections, including sarcoidosis, tuberculosis, coccidioidomycosis, candidiasis, Pneumocystis jiroveci, and rarely cryptococcosis (6). The present patient had an elevated 1,25(OH)2D level, pulmonary cryptococcosis and papillary thyroid carcinoma (PTC) simultaneously. Despite probable PTHrP expression in PTC (7) and unavailable PTHrP measurement, we could exclude hypercalcemia of malignancy for the following reasons. First, hypercalcemia was resolved without recurrence and 1,25(OH)2D value decreased to within the normal range after therapy targeted toward pulmonary cryptococcosis. Second, patients with humoral hypercalcemia of malignancy display a reduced serum 1,25(OH)2D level (8-10). In the study by Horwitz et al., serum 1,25(OH)2D was stimulated poorly by continuous 1,25(OH)2D concentration associated with pulmonary cryptococcosis in an HIV-negative, non-uremic patient. Hypercalcemia associated with infection by Cryptococcus neoformans and Coccidioides immitis. Am J Med Sci 318: 71-76, 1999.

The authors state that they have no Conflict of Interest (COI).

References

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Figure 3. Video-assisted thoracoscopic lobectomy of the right middle lobe demonstrating Cryptococcus neoformans (black arrows) surrounded by clear halos (periodic acid-Schiff stain, ×200).

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