HTLV-1-Associated Adult T Cell Leukemia Lymphoma Presenting as Granulomatous Pneumocystis Jiroveci Pneumonia (PJP) and Hypercalcemia

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BACKGROUND: Since the initial description of human T cell lymphotropic virus (HTLV-1), clusters of this infection have been detected globally. Unlike HIV infection, most patients infected with HTLV-1 remain asymptomatic throughout their lifetime.

CASE REPORT: We report the case of a 39-year-old Afro-Caribbean man with HTLV-1 infection presenting as hypercalcemia and granulomatous pneumocystis jiroveci pneumonia.

RESULTS: Interestingly, the hypercalcemia presented with normal parathyroid hormone–related protein and low 1,25 dihydroxyvitamin D levels, and the presence of pneumocystis jiroveci in the granulomas was diagnosed with transbronchial biopsy taken during bronchoscopy. HTLV-1-associated adult T cell leukemia lymphoma (ATLL) was diagnosed in this patient by bone marrow and lymph node biopsy.

CONCLUSION: Increased bone resorption, likely cytokine-mediated, is the most likely mechanism of hypercalcemia in this patient. This is believed to be the first description of this type of reaction to pneumocystis jiroveci in a HTLV-1-infected ATLL patient.

KEY WORDS: hypercalcemia; HTLV-1; granulomatous PJP; PTHrP; $1,25(OH)_2$ vitamin D; ATLL.
DOI: 10.1007/s11606-006-0047-6
 2007;22:420–423

INTRODUCTION

Since the initial description of human T cell lymphotropic virus (HTLV-1), clusters of this infection have been detected in Japan (seroprevalence 1–20%), the Caribbean, the Southwestern United States, Sub-Saharan Africa, Iran, and Europe.[1,3–8] Unlike HIV infection, most patients infected with HTLV-1 remain asymptomatic throughout their lifetime.[1,7] Adult T Cell leukemia lymphoma (ATLL) is a clinical manifestation of HTLV-1 infection. In addition, HTLV-1 is an etiologic agent for a progressive neurological disease called HTLV-1-associated myelopathy/tropical spastic paraparesis.[9]

Hypercalcemia may be associated with HTLV-1 infection,[7,8,10–15] where increased bone resorption mediated by parathyroid hormone–related protein (PTHrP)[1,3,7,8,10–15] or lymphokines[10,11] has been implicated.

Ninety percent of patients with ATLL suffer from life-threatening pulmonary complications,[1,2] including opportunistic lung infections such as pneumocystis jiroveci pneumonia (PJP).[1,2,4,16] Although prior reports of granulomatous PJP have been described in HIV-negative patients with malignancy[17,18,19] or in patients receiving immunosuppressive treatment,[20,22–25] this pathologic manifestation of pneumocystis jiroveci has not been previously reported in HTLV-1 infection.

We report a case of HTLV-1 infection with granulomatous PJP on lung biopsy with a normal CD4 count and hypercalcemia with normal serum PTHrP and low 1,25 dihydroxyvitamin D ($1,25(OH)_2D$) levels. We believe that increased bone resorption, probably cytokine-mediated, is the most likely mechanism of hypercalcemia in this patient.

CASE REPORT

A 39-year-old Afro-Caribbean man, with no significant medical history, presented to Queens Hospital Center in March 2004 with complaints of weight loss, generalized weakness, and joint pain associated with decreased exercise tolerance for 3 weeks. The patient denied taking any medications, including over-the-counter preparations.

The physical examination was remarkable for a low-grade temperature of 99.2°F and for bilateral palpable, nontender, mobile axillary, and inguinal lymph nodes. The lungs were clear. Neurologically, the patient was alert and oriented to person, place, and time without any focal deficits. Strength testing revealed full power bilaterally in both the upper and lower extremities.

Laboratory values were notable for a white blood cell count of $11,700/mm^3$ and a hematocrit of 29.4%. Serum chemistry profile (see Table 1) was remarkable for sodium of 131 mEq/L, blood urea nitrogen 39 mg/dL, creatinine 3.5 mg/dL, calcium 17.2 mg/dL (8.5–10.5 mg/dL), serum albumin 2.7 g/dL, corrected serum calcium 18.2 mg/dL, and phosphate 2.5 mg/dL (2.5–4.9 mg/dL). The work-up for hypercalcemia revealed an intact parathyroid hormone level of 7.6 pg/mL (12–72), a PTHrP level of <0.7 pmol/L (<1.3), $1,25(OH)_2D$ level of 46 pg/mL (19–67), and an angiotensin-converting enzyme level of 61 U/L (67–99). A repeat serum $1,25(OH)_2D$ level was 5 pg/mL.

Received April 10, 2006
Revised September 25, 2006
Accepted October 10, 2006
Published online January 9, 2007

Table 1. Labatory findings and treatment intervention

Laboratory test	March 8, 2004 (at admission)	March 9, 2004	March 11, 2004	March 15, 2004	March 18, 2004	March 22, 2004 (at discharge)
BUN (8–22 mg/dL)	39	34	19	18	26	21
Creatinine (0.4–1.6 mg/dL)	3.5	3.3	2.3	2.1	1.9	2.0
Calcium (8.5–10.5 mg/dL)	17.2	15.2	13.7	19.8	12	12
Corrected calcium (mg/dL)	18.2	16.2	14.7	20.8	13	13
Sodium (136–152 mEq/L)	131	134	131	139	138	136
Phosphorus (2.5–4.9 mg/dL)		2.5				
1.25(OH)$_2$D (19–67 pg/mL)				5		
Alkaline phosphatase (30–115 U/L)	103					
Albumin (3.3–5.3 g/dL)	2.7					
Urine sodium (mEq/L)	24					
Urine potassium (mEq/L)	35					
Urine chloride (mEq/L)	19					
Treatment intervention		IV pamidronate 90 mg, 1 dose		IV pamidronate 60 mg, 1 dose	Prednisone 40 mg every day	

BUN = blood urea nitrogen, IV = intravenous, 1,25(OH)$_2$D = 1,25 dihydroxyvitamin D.

Serum and urine protein electrophoreses were normal. Antibodies to HTLV-I/II tested positive. The CD4 helper T cell count was 1,717/mm^3 (515–1,595), the CD8 suppressor T cell count was 530/mm^3 (237–928), and the CD4/CD8 ratio was 3.24 (0.90–2.90). Antibodies to HIV were negative. The peripheral blood smear showed atypical lymphocytes with irregular nuclear borders described as "clover leaf."

A bone marrow biopsy revealed atypical lymphocyte infiltration. Flow cytometry of the bone marrow biopsy revealed that the majority of cells were immunoreactive for CD45, CD2, CD3, CD4, and CD30, whereas the expression of CD5 and CD7 was greatly reduced compared to CD2 and CD3. CD8 positive cells were only rudimentarily present. The strong presence of CD2, CD3, and CD4 coupled with the much weaker immunoreactivity of CD7 and CD8 was consistent with a diagnosis of ATLL. An axillary lymph node biopsy was also consistent with the diagnosis of ATLL.

Chest roentgenogram revealed fine diffuse reticulonodular densities, which were confirmed with a computed tomography scan of the thorax. Bilateral axillary node enlargement was also demonstrated. A skeletal survey revealed osteoporosis of the peripheral skeleton.

The patient underwent bronchoscopy with left lower lobe transbronchial biopsy, which revealed lung parenchyma with necrotizing and nonnecrotizing granulomas that stained positive for pneumocystis jiroveci (Gomori methenamine silver stain) and negative for acid-fast bacilli. Bronchoalveolar lavage fluid showed a CD4 helper T cell count of 60 U and CD8 suppressor T cell count of 37 U, with a normal CD4/CD8 ratio of 1.62. Neither acid-fast bacilli nor pneumocystis jiroveci organisms were present in the bronchoalveolar lavage fluid.

The hypercalcemia was treated with intravenous (IV) hydration, furosemide, pamidronate, and calcitonin. With hydration alone (using IV normal saline), the corrected serum calcium dropped by 2 mg/dL over the first 24 hours. Ninety milligrams of IV pamidronate was subsequently started, and the corrected serum calcium dropped an additional 2 mg/dL to 14.7 mg/dL over the next 2 days (see Table 1). At this point, the serum creatinine had dropped from 3.5 to 2.3 mg/dL. Intravenous hydration was continued and an additional dose of 60 mg of IV pamidronate was given 6 days after the first dose, with a further reduction in serum calcium level. Eleven days after admission, the corrected serum calcium level had dropped to 12.5 mg/dL and the serum creatinine was 1.8 mg/dL. The patient's symptoms improved. Treatment for PJP was started. Of note, when prednisone 40 mg daily was added there was no further decrease in the patient's serum calcium level (see Table 1). The hyponatremia seen on admission (131 mEq/L) corrected to near normal levels after a day of IV hydration, suggesting the etiology of the hyponatremia was dehydration. The admission course was complicated by a displaced fracture of the right patella that occurred while the patient was walking.

DISCUSSION

ATLL, a malignancy of helper/inducer T lymphocytes, is associated with HTLV-1 infection. Clinically, ATLL may present as leukemia, lymphoma, hypercalcemia, tumor infiltrates of the skin or lungs, hepatosplenomegaly and lytic bone lesions.[1,2] Most patients studied with HTLV-1-associated T cell

lymphomas have developed a syndrome of increased bone turnover and hypercalcemia at some time during the course of the disease.[1–3,5,7,8]

The mechanism for hypercalcemia has been described as increased bone resorption mediated by PTHrP or lymphokines, such as interleukin 1 (IL-1), IL-2, IL-6, and tumor necrosis factor (TNF).[10,12] Although the PTHrP level was not elevated in our patient, and IL levels were not measured, the mechanism for hypercalcemia was very likely increased bone resorption as evidenced by the rapid response to IV pamidronate. Although this patient did not have a bone density test to formally diagnose osteoporosis, the occurrence of the pathological fracture of the right patella may be because of this state of increased bone resorption. The high normal level of serum alkaline phosphatase (see Table 1) suggests that increased resorption of bone was taking place.

Although hypercalcemia has been reported in PJP, the underlying mechanism described is increased $1,25(OH)_2D$ production by the granulomatous tissue,[24,25] and this level was low in our patient, indicating that PJP was not the cause of hypercalcemia in this patient. Furthermore, the relatively low serum phosphorus level and the lack of response to prednisone in terms of a lowering of serum calcium both argue against excess $1,25(OH)_2D$ as the etiology of the hypercalcemia.

ATLL, the aggressive form of HTLV-1 infection, has long been recognized as a cause of immunosuppression and opportunistic infections, including PJP.[16] In contrast to HIV infection, where CD4 counts can be used as a measure of immune deficiency because of profound depletion in the number and function of these cells, HTLV-1 infection and ATLL are characterized by proliferation of dysfunctional CD4 cells.[4–7] Only a few reports of pneumocystis jiroveci infection have been reported in HTLV-1 carriers, and none of them have presented as granulomatous inflammation.

Granulomatous PJP has rarely been described in patients with malignancy and immunosuppression because of chemotherapy or high-dose corticosteroids.[17,19,26] This pathological reaction poses a diagnostic challenge, as it mimics other granulomatous diseases.[17,18,21] The development of granulomatous PJP in our patient with HTLV-1 infection and a normal CD4 count may be related to partial immunosuppression with preservation of immune cell number and adequate production of IL-2, interferon gamma, and TNF alpha, all crucial factors in granuloma formation.

This is the first case reported in the literature of granulomatous PJP occurring in a patient infected with HTLV-1. There is not a lot of information in the literature concerning the typical presentations of PJP in patients who have HTLV-1. There are, however, two relevant case reports. In one report a patient had patchy, nonsegmented bilateral infiltrates.[27] In another patient, there was a diagnosis of pneumonia caused by PJP, mycoplasma, mycobacterium avium-intracellulare, and cryptococcus. The presentation was lobar infiltrates, pleural effusion, patchy alveolar infiltrates, and mediastinal adenopathy.[4] Interestingly, the hypercalcemia in our patient occurred in the setting of normal PTHrP and low $1,25(OH)_2D$ levels, supporting the role for cytokines in the development of HTLV-1-related hypercalcemia. Specific cytokines were not measured on this patient, and this may represent a limitation of our paper. The possibility of PTHrP acting as a cytokine, causing bone destruction and hypercalcemia, even with normal serum levels of PTHrP, has been described in breast cancer.[28] Whether this phenomenon can occur in HTLV-1-associated hypercalcemia is not known.

This case reminds us that patients with HTLV-1 infection may have many reasons to present with hypercalcemia. We believe the reason for the hypercalcemia in our patient was increased bone resorption.

Potential Financial Conflicts of Interests: *None disclosed.*

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