

## CLINICAL VIGNETTE

# Hypercalcemia and *Strongyloides stercoralis* hyperinfection in A patient with Adult T-cell lymphoma/leukemia (ATL)

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### Case Report

Adult T-cell leukemia/lymphoma (ATL) is an uncommon hematologic malignancy in the United States. Patients with ATL may manifest a broad spectrum of presentations, ranging from nonspecific constitutional complaints to profound lymphadenopathy and hepatosplenomegaly. Serologic testing of viral antigens has linked ATL to infection with HTLV-1, the Human T-lymphotropic virus<sup>1,2</sup>. Worldwide, HTLV-1 infection occurs in 15 to 20 million people; the highest prevalence is in Japan, where up to two million people are infected<sup>3,4</sup>. The prevalence in the United States is considerably smaller. Even with combination chemotherapy, patients with aggressive ATL are highly susceptible to opportunistic infections, including *Strongyloides* and *Pneumocystis*. The median survival of ATL is four years, although survival for advanced subtypes is less than one year<sup>5</sup>.

We present a patient with newly diagnosed ATL whose hospital course was complicated by *Strongyloides stercoralis* hyperinfection and refractory hypercalcemia, both of which contributed to the patient's death despite aggressive chemotherapy.

### Case Summary

A 55-year-old male immigrant from Belize presented to our institution with one week of altered mental status, decreased oral intake and low back pain. Two months prior to this, he had been admitted for abdominal pain; stool studies identified *Strongyloides stercoralis* infection for which he was prescribed ivermectin. Between these two hospitalizations, he reported a 15-pound involuntary weight loss and continual night sweats and chills.

At the time of the patient's second admission, he was afebrile, normotensive and mildly tachycardic. He appeared cachectic and lethargic. His mucous membranes were dry and he was oriented only to self. His abdominal exam revealed bilateral inguinal lymphadenopathy.

Laboratory studies on admission were notable for a serum creatinine of 4.5 mg/dL, blood urea nitrogen 60 mg/dL, serum calcium 18.2 mg/dL, total protein 7.1 g/dL, albumin 2.7 g/dL and alkaline phosphatase 309 U/L. His serum lactate dehydrogenase was 535  $\mu\text{mol/L}$  (normal 109-230  $\mu\text{mol/L}$ ). Serum and urine protein electrophoreses with immunofixation did not reveal a monoclonal protein. Serum free light chain assays were unremarkable. A urinalysis revealed 1+ proteinuria. A computed tomography scan of the chest, abdomen and pelvis showed consolidation in the left upper lobe and lytic lesions throughout the ribs, pelvis and spine, but did not identify any masses or lymphadenopathy (Figure 1). A bone marrow biopsy was performed on hospital day 2 from an anterior approach due to the patient's inability to cooperate, but the specimen was not diagnostic for hematologic malignancy.

The patient's severe hypercalcemia persisted despite pamidronate, calcitonin and aggressive fluid hydration. He also developed marked leukocytosis. A repeat bone marrow biopsy and aspirate was performed on hospital day 15 which showed cellularity ranging 10 to 85 percent and areas of lymphoid cells with irregular nuclei. The patient's peripheral blood smear demonstrated circulating atypical lymphocytes morphologically resembling "flower cells" with a CD4+/CD25+ immunophenotype. Subsequent enzyme-linked immunoassay and Western blotting confirmed HTLV-1 infection.

Due to refractory hypercalcemia and leukocytosis, the patient was treated with dexamethasone. He subsequently developed respiratory distress and was transferred to the intensive care unit. A bronchoscopy with bronchoalveolar washings and repeat stool studies identified *Strongyloides stercoralis*. The patient's respiratory decompensation was attributed to *Strongyloides* hyperinfection syndrome and the patient began anti-helminthic therapy with

ivermectin. Hepatitis B infection was also identified by serologies for which entecavir was initiated.

On hospital day 23, the patient received combination chemotherapy with cyclophosphamide, vincristine, doxorubicin and prednisone (CHOP). After an initial hematologic response with a decrease in lymphoma cells in the peripheral blood over several days, the patient's lymphocytosis and hypercalcemia recurred (Figure 2). The patient subsequently developed severe sepsis complicated by lactic acidosis and myocardial infarction. He was placed on comfort measures and expired on hospital day 39.

### Discussion

ATL is a T-cell lymphoid neoplasm with varying clinical presentations based on the subtype of disease. HTLV-1 infection is central to the pathogenesis of ATL, which is strongly associated with areas endemic to HTLV-1 such as Japan, the Caribbean, western Africa and Peru. Although the leukemogenesis of HTLV-1 is not fully understood, expression of the viral transactivator protein Tax seems to play a pivotal role in T-helper cell dysregulation<sup>6</sup>. Transmission of HTLV-1 occurs through blood or sexual contact. The virus may also be transmitted transplacentally and through breast milk. Of the modes of transmission, breastfeeding has been associated with the highest risk of developing ATL<sup>7</sup>. Although development of ATL requires HTLV-1 infection, only five percent of HTLV-1-positive individuals develop the malignancy, usually 10 to 30 years following infection.

There are four identified subtypes of ATL: indolent (smoldering), chronic, lymphomatous and leukemic (acute)<sup>8</sup>. Smoldering ATL develops slowly with mild manifestations such as cutaneous lesions. Patients have a low number of leukemic cells (one to five percent abnormal peripheral blood lymphocytes). The chronic subtype also develops slowly but demonstrates a high leukocyte count with lymphadenopathy and cutaneous lesions. Historically, the smoldering and chronic subtypes have been monitored without therapy, as the median survival for both subtypes typically exceeds two years without treatment<sup>6</sup>.

The leukemic and lymphomatous subtypes are more common but also more aggressive, with median survivals ranging from eight to 10 months. Massive lymphadenopathy, leukocytosis, hepatosplenomegaly, hypercalcemia and osteolytic bone lesions characterize these two subtypes. The main distinction between the leukemic and lymphomatous subtypes is the absence of peripheral blood involvement in the

lymphomatous form. Therapy for these aggressive ATL subtypes historically involved combination chemotherapy, usually CHOP, although recent studies suggest initiating antiviral therapy with zidovudine (ZDV) and interferon (IFN) in acute subtypes.

Diagnosis of ATL is established by a combination of HTLV-1 infection and characteristic immunophenotyping of malignant cells. These cells express surface T-cell markers CD2, CD4 and CD5, and are usually negative for CD7, CD8 and CD26. ATL cells also exhibit expression of CD25, the lymphocyte activation marker<sup>6</sup>. Examination of the peripheral blood reveals pathognomonic "flower cells," pleomorphic cells with indented nuclei.

Patients with ATL invariably develop immunosuppression, and opportunistic infections are often a presenting feature. *Strongyloides* hyperinfection syndrome manifests as fever with gastrointestinal or pulmonary abnormalities. Severe cases may lead to organ failure and septic shock. The propensity for *Strongyloides* infection has been attributed to decreased T-helper type immune responses due to HTLV-1 infection<sup>9</sup>. While ivermectin is the standard anti-helminthic agent, patients with ATL have poorer responses due to profound immunosuppression from both ATL and chemotherapy. Patients with ATL are at increased risk for other opportunistic infections, including *Pneumocystis*.

Our patient exhibited a classic presentation of the leukemic subtype of ATL, including lymphocytosis with flower cells, osteolytic lesions with hypercalcemia, lymphadenopathy and *Strongyloides* infection. In spite of anti-helminthic therapy and combination chemotherapy, our patient expired from rapidly progressive disease.

### Key Teaching Points

Although relatively rare in the United States, ATL may be diagnosed in institutions with a significant immigrant population from Japan or the Caribbean. While no single clinical feature is pathognomonic, diagnosis of ATL should be strongly considered in patients who manifest any of the following constellations of findings:

1. History of opportunistic infection, including *Strongyloides* or *Pneumocystis*
2. Lytic bone lesions and hypercalcemia occurring with lymphadenopathy and/or lymphocytosis
3. History of travel to or immigration from HTLV-1-endemic areas such as Japan, Africa, Peru and the Caribbean

4. Peripheral blood examination showing “flower cells” and immunophenotyping demonstrating expansion of T-lymphocyte markers CD2, CD4, CD5 and CD25
5. HTLV-1 infection.

The current recommended therapy for this disease depends upon the ATL subtype and are summarized as follows<sup>6</sup>:

- Acute: Induction and maintenance therapy with combination ZDV with IFN; followed by allogeneic hemato-poietic stem cell transplantation, if feasible. Recent studies have shown only a marginal benefit with cytotoxic chemotherapy.
- Lymphomatous: Induction with CHOP and ZDV/IFN, maintenance with ZDV/IFN with allogeneic stem cell transplantation, if feasible.
- Chronic or Smoldering: ZDV/IFN.

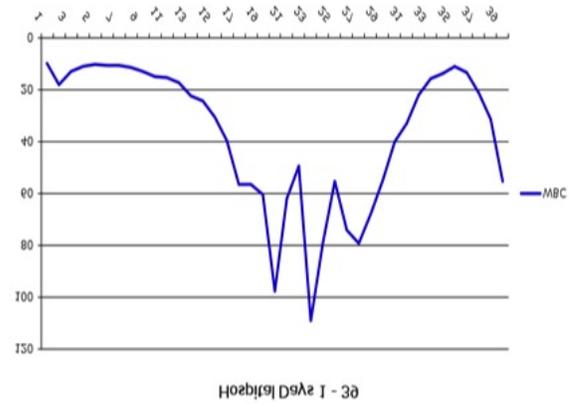


Figure 2: WBC vs. hospital day. Note that Cycle #1 CHOP was started on Day 23.

4-year survival	2%	0%	0%	51%
Median survival	6 mos	10 mos	>4 years	54 mos
Proportion of ATL cases	22%	50%	2%	50%
	Acute	Lymphomatous	Smoldering	Chronic

Table 1: Prevalence and survival of ATL subtypes.

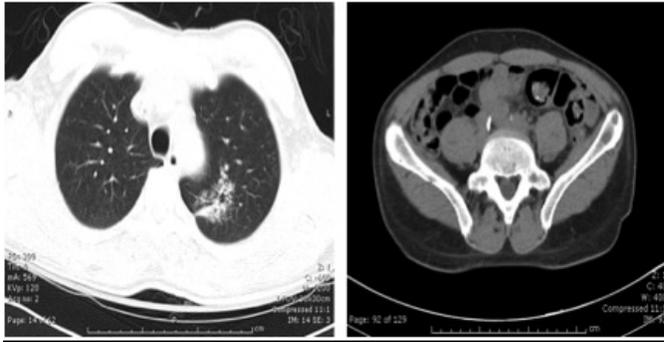


Figure 1: Left panel shows computed tomography (CT) scan of the chest with left upper lobe consolidation due to *Strongyloides* pneumonia. Right panel shows CT scan of abdomen with lytic lesions involving the spine and pelvis.

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