A Case of Hypercalcemia due to Adult T-Cell Lymphoma

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ABSTRACT

Adult T-cell leukemia (ATL) is the only T-cell lymphoproliferative disease, known to be caused by a virus. While human T-lymphotropic virus type 1 (HTLV-1) is found to cause adult T-cell leukemia, other T-cell neoplastic diseases do not correlate with human T-lymphotropic virus type 1. Adult T-cell leukemia usually demonstrates an aggressive course and poor prognosis. Human T-lymphotropic virus type 1 is transmitted via breast feeding, sexual contact, shared needles, and infected blood products. Moreover, some geographic areas are depicted to be endemic for human T-lymphotropic virus type 1; northeast of Iran is known to be one. Here in, a case of adult T-cell leukemia is discussed who presented by hypercalcemia and paraparesia. Hepatosplenomegaly was detected in physical examination and abdominal sonography revealed multiple para-aortic lymphadenopathy. Whole body bone scan demonstrated multiple hot points in skeleton. Chest computed tomography (CT) scan revealed leukemic infiltrations of both lungs. The leukocyte count of peripheral blood was 34000-50000 per mm3, and excessive amounts of mature lymphocytes were observed in peripheral smear. Flow cytometry of bone marrow aspiration reported adult T-cell leukemia. The titer of human T-lymphotropic virus type 1 antibody was elevated in enzyme-linked immunosorbent assay (ELISA) method. Despite the patient was originated from a non-endemic origin, all members of his family including his spouse and children found to be positive for human T-lymphotropic virus type 1. This manuscript describes the clinical course and diagnosis of a patient with adult T-cell leukemia, and clinical suspicions during the course of the disease.


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Introduction

Adult T-cell leukemia (ATL) is known to be an aggressive type of non-Hodgkin lymphoma (NHL), caused by infection with human T-Lymphotropic virus type 1 (HTLV-1) (1). HTLV-1 infection is presumed to be endemic in some specific geographic regions such as western Africa, Southern Japan, and northeast of Iran (1-3). Thus, prevalence of ATL is assumed to be diverse following endemic predisposition.

HTLV-1 is transmitted via blood transfusion, sexual contact, breast feeding, and shared needles (4-6). A few percent of infected people will develop ATL (as much as 5%) and several decades are mentioned as latent period (7).

ATL is defined to have variant clinical courses and thus, classified to acute, chronic, lymphomatous, and smoldering subtypes (8, 9). Median survival rate is variable ranging from few months in acute subtype up to 3-5 years in smoldering and chronic types (9, 10).

Clinical manifestations of ATL include leukocytosis with predominant lymphocyte counts, lymphadenopathy, hepatosplenomegaly, and skin lesions. Hypercalcemia, opportunistic infections, and lytic bone lesions are among the presentations (11-13). Tropical spastic paraparesis may accompany manifestations of ATL; a myelopathy known to be caused by HTLV-1 infection (14).

The key point in diagnosis of ATL is a high index of suspicion regarding the clinical symptoms and the patient’s origin. Peripheral blood smear of patients with ATL may reveal medium-sized lymphocytes with lobate nuclei, and condensed chromatin resembling a flower (flower cells) (15). Lymph node biopsy may reveal a diverse range of changes and so, is not such diagnostic (16). ATL cells present CD2, CD5, CD4, CD25, and CD52 in immunophenotyping, while CD7 and CD8 are usually lacking (16, 17). HTLV-1 infection is diagnosed through specific antibody detection through enzyme-linked immunosorbent assay (ELISA) method, and detecting viral load via polymerase chain reaction (PCR) (18, 19).

Herein, a patient with newly diagnosed ATL is presented.

Case Report

A 64-year-old man was presented to emergency department with delirium. He was reported to have ambulation disability, severe low back pain, and urinary incontinence during recent weeks. A history of significant weight loss and loss of appetite was present. No history of polyuria and polydipsia was found. He had a car accident in recent month. His family was originated from Neyshabour City, northeast of Iran. He denied any history of smoking, drug use or alcohol consumption.

In physical exam, he was disoriented and lethargic. A low-grade fever and tachycardia was detected. A blood pressure of 140/80 mmHg, and respiratory rate of 18 per minute were measured. Crackles and rhonchi were auscultated in both lungs. Splenomegaly was found, and liver span was enlarged up to 18 centimeters. Bilateral inguinal lymphadenopathy was palpated with a firm and non-tender consistence. No genital ulcer was detected. Severe tenderness was revealed in vertebrae percussion in lower thoracic and lumbar level and thus, hard backboard was applied.

Primary medical care was performed and essential laboratory tests were ordered. The results are listed in table 1.

Abdominal ultrasonography revealed non-huge hepatosplenomegaly with normal size kidneys. Intra-abdominal lymphadenopathy was not reported.

Intensive and prompt hydration was performed due to patient's hypercalcemia, and since the correction rate was not satisfying, temporary hemodialysis and bisphosphonate were administered. Serum calcium level was controlled and investigations were initiated. Parathyroid hormone (PTH) level was suppressed (3.5 pg/ml with a normal range of 9-94), and normal 25-OH vitamin D level was detected.
Table 1. Laboratory tests of the patient at presentation

<table>
<thead>
<tr>
<th>WBC: 35500 /mm³</th>
<th>Na: 137 meq/l</th>
<th>AST: 44 IU/l</th>
<th>U/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb: 11.2 g/dl</td>
<td>K: 3.7 meq/l</td>
<td>ALT: 19 IU/l</td>
<td>SG: 1020</td>
</tr>
<tr>
<td>MCV: 87.6 fl</td>
<td>BS: 91 mg/dl</td>
<td>ALP: 1680 IU/l</td>
<td>Bacteria: Negative</td>
</tr>
<tr>
<td>Plt: 379000 /mm³</td>
<td>Urea: 161 mg/dl</td>
<td>Bilirubin total: 1 mg/dl</td>
<td>pH: 5</td>
</tr>
<tr>
<td>PTT: 26 s</td>
<td>Cr: 3.8 mg/dl</td>
<td>Bilirubin direct: 0.6 mg/dl</td>
<td>Glucose: Negative</td>
</tr>
<tr>
<td>PT: 12.5 s</td>
<td>Ca: 11.4 mg/dl</td>
<td>LDH: 726 IU/l</td>
<td>Blood: Positive</td>
</tr>
<tr>
<td>INR: 1</td>
<td>Alb: 2.6 g/dl</td>
<td>CPK: 85 IU/l</td>
<td>Nitrite: Negative</td>
</tr>
<tr>
<td>Uric Acid: 7.2 mg/dl</td>
<td>P: 5.3 mg/dl</td>
<td>ESR: 37 mm/hour</td>
<td>WBC: 4-6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RBC: 10-12</td>
</tr>
</tbody>
</table>

WBC: White blood cell; Hb: Hemoglobin; MCV: Mean cell volume; Plt: Platelet; PTT: Partial thromboplastin time; PT: Prothrombin time; INR: International normalized ratio; Na: Sodium; K: Potassium; BS: Blood sugar; Cr: Creatinine; Ca: Calcium; Alb: Albumin; P: Phosphorus; AST: Aspartate transaminase; ALT: Alanine transaminase; ALP: Alkaline phosphatase; LDH: Lactate dehydrogenase; CPK: Creatine phosphokinase; ESR: Erythrocyte sedimentation rate; RBC: Red blood cell

Increased level of alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) raised the suspicion to malignancy; solid vs. hematologic gamma-glutamyl transferase (GGT) level was normal.

Prompt antibiotic therapy was initiated with a clinical diagnosis of sepsis and a peripheral blood smear was provided. Abundant presence of moderate sized lymphocytes was observed in the smear, and chronic lymphocytic leukemia (CLL) was proposed as the diagnosis (Figure 1). However, after restudy of data, in second look convoluted nuclei were observed in a number of lymphocytes, resembling "flower cells". Then, the flow cytometry of peripheral blood was done.

![Peripheral blood smear (× 100)](image)

Computed tomography (CT) scan of spinal cord was done, revealing diffuse infiltration of lower thoracic and lumbar vertebrae without apparent collapse or wedge fracture. Skull X-ray was captured with no obvious abnormality. Serum protein electrophoresis and immunofixation were done to consider multiple myeloma, which was ruled out. Bone scintigraphy scan was recommended. It reported heterogeneous uptake in all ribs, thoracolumbar vertebrae, and pelvic bones, which suggested multiple bone metastases. Prostate serum antigen (PSA) and free PSA was measured which was reported to be normal.

Chest CT scan was performed; revealing air space opacities, peripheral centri-acinar nodules, and peribronchial thickening. Leukemic infiltration of the lungs vs. bronchopneumonia was proposed. A few mediastinal lymphadenopathies were reported.

In spite of negative urine and blood cultures, consciousness was improved following antimicrobial therapy. Serum creatinine was decreased to 1.6 mg/dl, and serum calcium level reached 7.4 mg/dl with a serum albumin level of 2.9 g/dl.

Contrary to the primary diagnosis proposed as CLL, flow cytometry reported T-cell leukemia resembling Sezary cells. Surface cellular markers included CD4, CD5, and CD25; while CD19, CD20, CD7, and CD8 were absent.

Investigations for detecting HTLV-1 infection were carried out, due to flow-cytometry results and patient's origin. Anti-HTLV-1 IgG antibody was measured and reported to be positive with a titer of 2.4
The result was confirmed with rechecking. Finally, ATL was emerged. In further assessments, all members of his family including his spouse and children found to be positive for human T-lymphotropic virus type 1.

Discussion
Elevated leukocyte counts, as many as 20000 per mm$^3$, should raise the suspicion to hematologic dyscrasia. Peripheral blood smear is a crucial tool to propose a primary diagnosis. However, gross cellular morphology of ATL is sometimes misleading, resembling CLL. The physician should be aware of pathognomonic morphologies such as “flower cells” with large nuclear-cytoplasmic (N/C) ratio, condensed chromatin and convoluted nuclei.

Our patient was presented with hypercalcemia. After confirmation, PTH level was requested in order to approach to patient’s high calcium level. Because of suppression of PTH level, malignancy-related hypercalcemia was suspected.

Hypercalcemia is a common complication in ATL, reported to be prevalent as 40% (17). Lytic bone lesions may accompany or not. Serum calcium level may rise up to 20 mg/dl and hypercalcemia-induced symptoms may ensue, including confusion and polyuria. Hypercalcemia in presented case did not respond to hydration alone, and necessitated hemodialysis and administration of pamidronate. Hypercalcemia was controlled thereafter, and serum creatinine level was decreased gradually, reaching to 1.7 mg/dl.

ATL is classified as high-risk leukemia for developing tumor lysis syndrome (TLS). Sufficient hydration, and uric acid and electrolytes monitoring should be considered. Interestingly, some studies recommend initiating rasburicase prophylactically. Either of uric acid elevation, hyperphosphatemia, hyperkalemia, and hypocalcemia warns TLS and demands prompt intervention including excessive hydration, rasburicase administration, and hemodialysis, if indicated (20). Uric acid and electrolytes levels were checked repeatedly in our patient. Nonetheless, no abnormality was detected (except hypercalcemia). However, the patient was undergone hemodialysis because of refractory hypercalcemia.

A study of chest CT scans of 60 patients with ATL demonstrated variable abnormalities in 69% of patients. Ground glass opacities, centrilobular nodules, and increased bronchovascular bundles especially in periphery of lungs (21). Disperse consolidations, peripheral centri-acinar nodules and peribronchial thickening were reported in our patient. These manifestations seem to be non-specific. However, they should be considered in the setting of ATL, after infectious etiologies were ruled out.

HTLV-1-associated myelopathy (HAM) or tropical spastic paraparesis (TSP) was observed in infected patients with a variable latent period ranging from months to decades (22). The clinical course is insidious, and it occurs more common in women (23). Proximal weakness of lower limbs, sphincter disturbances such as urinary incontinence, frequency or retention, paresthesia, and lower back pain are among the symptoms. Hyperreflexia, upward plantar reflex, clonus, disturbed vibration sense, and exaggerated jaw jerk are reported in neurological exam of HAM (24). Imaging of central nervous system (CNS) may lack any abnormality. Viral load of HTLV-1 is utilized as a diagnostic tool. Moreover, antibody titer of cerebrospinal fluid (CSF) may be helpful as CSF/serum antibody ratio will be increased in HAM (25). Anti-viral treatment has not depicted any significant benefit, while corticosteroid administration caused relative improvement (26). Upward plantar reflex and hyperreflexia were found out in this case. CNS imaging did not report any significant abnormality in vertebrae structure. Lumbar puncture was not performed. However, high-dose dexamethasone was administered, leading to slight improvement in neurological symptoms.
The patient was referred to a hematologist to decide about proper treatment and selection of appropriate chemotherapy regimen.

Conflict of Interests
Authors have no conflict of interests.

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