


HTLV-I-Associated Lymphoma Presented as Massive Lymphadenopathy

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Abstract

Adult T-cell leukemia/lymphoma is an aggressive T-cell malignancy caused by the long-term infection of human T-cell lymphotropic virus type I (HTLV-I). Our understanding of clinical features still largely relies on the Shimoyama classification developed 30 years ago, which described the 4 clinical subtypes (the smoldering, chronic, lymphoma, and acute types) based on the manifestations of lymphocytosis, elevated lactate dehydrogenase, hypercalcemia, lymphadenopathy, and involvement of the skin, lung, liver, spleen, central nervous system, bone, ascites, pleural effusion, and gastrointestinal tract. HTLV-I-associated lymphoma has a variety of presentations but the presentation of massive lymphadenopathy and compression symptoms is rare and has not been emphasized in the literature. In this article, we describe 2 cases of adult T-cell leukemia/lymphomas that presented with massive cervical nodes or mediastinal nodes with compressing symptoms as the major presenting clinical features. Clinicians should remain aware of this type of presentation by HTLV-I-associated lymphoma, especially in patients who came from endemic areas, even if not all clinical features are present and particularly with hypercalcemia and lytic bone lesions.

Keywords

human T-cell lymphotropic virus type I-associated lymphoma, HTLV-I, lymphadenopathy

Introduction

Adult T-cell leukemia/lymphoma (ATL) is a rare and aggressive mature T-cell malignancy caused by chronic infection with human T-cell lymphotropic virus type I (HTLV-1).¹ Globally, there are 20 million people infected with HTLV-1. Most of these cases involve residents of Southern Japan, Africa, the Caribbean areas, Central and Latin America, Romania, the Middle East, Melanesia, and Central Australia, or immigrants from the above-mentioned areas.^{2,3} Because of the lifelong viral carrier state and long latency (20–40 years) after HTLV-1 infection, only a small proportion of the infective population will progress to ATL (2.1% for women and 6.6% for men).⁴ ATL can be classified into 4 subtypes (acute, lymphoma, chronic, and smoldering), presenting with diverse clinical features. Acute ATL is characterized by leukemic manifestations, lymphadenopathy, organomegaly, hypercalcemia, and related symptoms. Lymphoma ATL presents with the main lymphadenopathy with or without extranodal lesions but without lymphocytosis. Smoldering ATL is characterized by normal leukocyte count and infiltration in only the skin and lungs without the involvement of any other

viscera. Chronic ATL is associated with high leukocyte count, mild lymphadenopathy, and organomegaly, without elevated lactate dehydrogenase levels or visceral involvement.^{5,6} To our knowledge, the presentation of massive cervical lymphadenopathy and mediastinal lymph node mass has rarely been reported as a manifestation of ATL. On literature review, we identified only 3 previously reported cases.^{7,8}

Here, we present 2 cases of ATL with massive lymphadenopathy and severe compression symptoms, which have not been previously reported.

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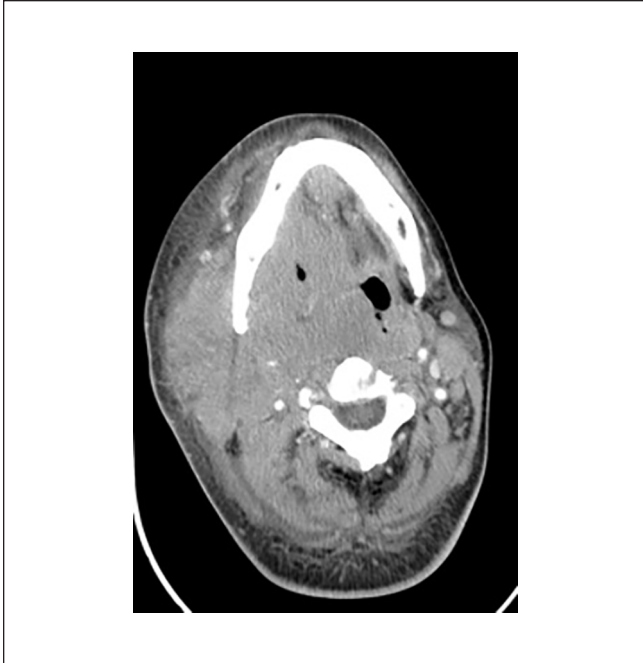


Figure 1. Axial computed tomography image of the neck shows a large soft tissue mass centered in the right nasopharynx, extending to the right tonsillar fossa and right parapharyngeal space.

Case Report 1

A 70-year-old Caribbean female with no prior medical or surgical history presented to the emergency department (ED) with complaints of difficulty breathing. Two months prior, she noticed a gradually enlarging right-sided oropharyngeal mass for which she was treated with amoxicillin as an outpatient for suspected nasopharyngeal infection. When presenting to the ED, she had stridor with drooling and was unable to provide any history. Urgent bedside fiber-optic evaluation noted narrowed upper airway with mass compression and inability to advance the probe. She underwent an emergent tracheostomy, and a biopsy of the mass was obtained. The initial vitals were within normal limits. Aside from the neck mass and audible stridor, there was no other pertinent finding on the physical examination.

Laboratory examinations revealed hypercalcemia (17.8 mg/dL) and elevated lactate dehydrogenase (LDH; 1807 IU/L; normal range = 313-618 IU/L). The patient was started on aggressive intravenous normal saline fluid, calcitonin and zoledronic acid for hypercalcemia. Computed tomography (CT) scan showed a large soft tissue mass extended to the right nasopharynx, the right tonsillar fossa and right parapharyngeal space, and bilateral necrotic lymph nodes and osseous metastatic lesion in the upper thoracic spine (Figure 1).

Biopsy of the mass noted high grade peripheral T-cell lymphoma—not otherwise specified with immunohistochemical markers positive for GATA-3, CD3, CD4, CD8, CD30,

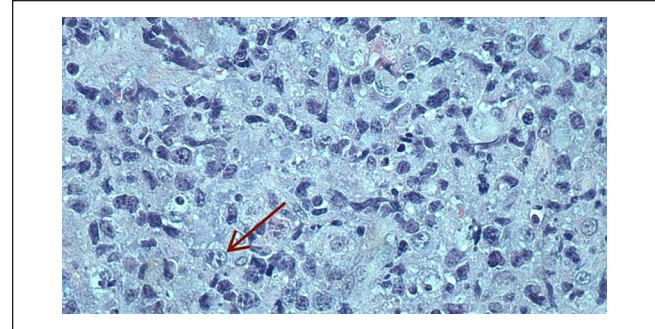


Figure 2. Case 1: Pharynx mass biopsy, hematoxylin-eosin stain, sheets of atypical large-sized lymphoid cells (arrow; 50× magnification).

CD45, and Ki-67, and negative for CD7, CD20, ALK-1, AE1/AE3, CK7, synaptophysin, chromogranin, CD56, TTF-1, and EBER (Figure 2). The biopsy specimen was then proven positive for HTLV-1 by polymerase chain reaction (PCR; done at Dr Tam Lab, Cornell Hospital, NY). Bone marrow was negative for lymphoma, and ENT consultation revealed no intrinsic nasopharyngeal mucosal lesions. Cerebrospinal fluid flow cytometry analysis was negative for lymphoma cells. The diagnosis was HTLV-1-associated lymphoma, lymphoma type. She was treated with 2 cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), but expired after 1 month, unfortunately.

Case Report 2

A 51-year-old Caribbean female with multiple medical comorbidities, including hypertension and systemic lupus erythematosus, presented to the ED with new-onset left facial swelling that started 2 weeks before presentation. She had a history of hospitalization 3 years previously for neck pain. She was found to have lytic lesions of the cervical and lumbar spine, bilateral axillary lymphadenopathy, and right hilar lymphadenopathy by CT scan, elevated uric acid, and elevated LDH (26800 IU/L). She had a bone biopsy in the right iliac crest (Figure 3) that revealed anaplastic large T-cell lymphoma with immunohistochemical marker positive for CD2, CD4, CD25, CD30, CD43, CD45, BCL-2, MUM-1, and Ki67 (90%), and negative for CD3, CD5, CD7, CD8, CD10, CD20, CD56, CD79a, CD138, ALK-1, EBER, BCL-6, Cyclin D1, and PAX-5. Serology showed positive for HTLV-1 antibody. Biopsy specimen of lymphoma was also positive for the HTLV-1 genome by PCR assay (Dr Tam Lab at Cornell Hospital). Therefore, she was diagnosed with HTLV-1-associated lymphoma, lymphoma type. The patient received 2 cycles of CHOP and 8 cycles of CHOEP (CHOP plus etoposide) with clinical remission with shrinkage of her lymphadenopathy.

Then, 1 year later, a positron emission tomography CT scan revealed progression of the disease with hypermetabolic cervical and mediastinal lymph nodes, liver, and

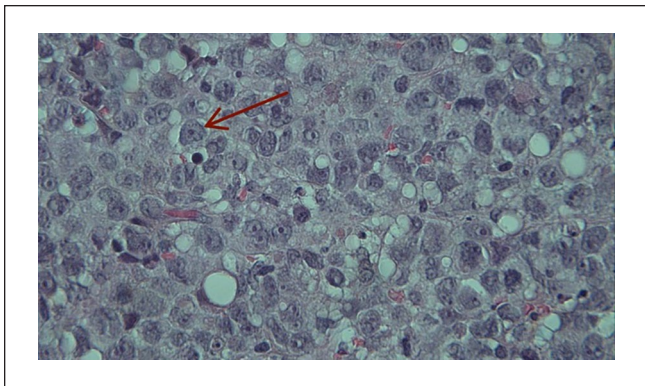


Figure 3. Case 2: Bone marrow core biopsy, hematoxylin-eosin stain, markedly hypercellular marrow (>90%) with diffuse atypical lymphoid infiltrate (arrow; 50× magnification).

osseous lesions. She was then started on brentuximab until the second year after the original diagnosis. Repeat positron emission tomography scan post-chemotherapy noted almost complete resolution, and then the patient had a bone marrow transplant. Three years after the original diagnosis, the patient came to the emergency room for left facial, tongue, and left neck and shoulder swelling. The vitals were within normal limits. Physical examination revealed left facial and neck swelling and lymphadenopathy of left supraclavicular and left axillary. Laboratory findings showed elevated LDH, 1133 IU/L (normal range = 313-618 IU/L). CT scan of neck noted mild bilateral cervical and supraclavicular lymphadenopathy with abnormal increasing soft tissue density in the mediastinum and right hilum with compression of the superior vena cava (Figure 4). The mixed lytic and sclerotic appearance of the spine suggested metastases with multiple chronic compression fractures. CT scan of the abdomen and pelvis revealed diffuse sclerotic and lytic changes across the entire lumbar spine, lower thoracic, and pelvis. Magnetic resonance imaging of the thoracic and lumbar spine noted extensive metastatic disease. The patient was urgently taken to the operation room for stenting of the superior vena cava. However, the patient was discharged after she refused further treatment and expired 4 months after discharged.

Discussion

ATL is an aggressive peripheral T-cell malignancy with a distinctly poor prognosis that was first recognized globally in 1977 through a report of 16 cases of ATL patients in southwestern Japan.⁹ HTLV infection has been identified as the cause of ATL through the highly coincident co-localization of the areas of ATL cases and HTLV endemic regions.² Although there are still many to be discovered, the biological functions of viral genes, alterations of cellular genes associated with ATL, and somatic aberrations in ATL revealed through integrated genetic analysis have further confirmed

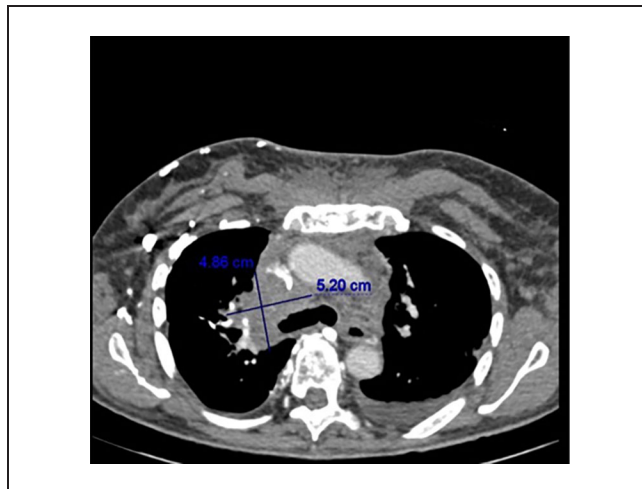


Figure 4. Axial computed tomography image of the superior chest showed abnormal increasing soft tissue density in the mediastinum and right hilum concerning for malignancy, with some compression of the superior vena cava.

the connection between ATL and HTLV and increased our understanding of the development of ATL.^{10,11} However, the study of ATL has been limited by the rarity of this disease. The lifetime risk of developing ATL is 1% to 5% among the 10 to 20 million HTLV-1 infected individuals worldwide, after a very long latency period that can exceed 50 years.^{2,12}

The subclassification of HTLV-1-associated ATL remains unchanged since Shimoyama developed a series of diagnostic criteria for the 4 clinical subtypes: acute, lymphoma, chronic, and smoldering.⁵ The majority of ATLs are aggressive types, acute leukemia and lymphoma, which account for 60% and 20%, respectively.¹³ These 2 types are characterized by lymphadenopathy, highly elevated LDH, hypercalcemia, extranodal lesions (such as bone, liver, spleen, CNS, gastrointestinal tract, skin, and lung infiltration), and symptoms related to the above manifestations. The acute type presents as leukemia, which is defined as lymphocytosis and more than 1% T lymphocytes in peripheral blood, while the lymphoma type presents mainly lymph node enlargement in the absence of peripheral blood involvement. The chronic and smoldering types are relatively indolent subtypes, accounting for 15% and 5% of all ATL, respectively. Smoldering ATL is characterized by skin or lung infiltration without any other visceral involvement, $\geq 5\%$ abnormal T lymphocyte in peripheral blood with normal leukocyte count. Chronic ATL presents with leukocytosis, lymphadenopathy, hepatomegaly, splenomegaly, skin, and pulmonary lesions with the absence of elevated LDH, hypercalcemia, and other visceral involvement.^{5,9,13,14}

Both of our cases presented with elevated LDH higher than 2 times the normal upper limit, lymphadenopathy, but no evidence of leukocytosis and no abnormal lymphocyte in peripheral blood. According to the Shimoyama classification,

both cases were most likely diagnosed with ATL lymphoma type.^{5,15} Case 1 presented with elevated LDH, hypercalcemia, and massive cervical lymphadenopathy causing compression of the airway, and esophagus, as well as the absence of leukocytosis and abnormal peripheral lymphocyte. Case 2 had a much longer disease process that lasts for 3 years. She presented with extremely high LDH, lymphadenopathy, bone infiltration, and the absence of leukemia. She got near complete resolution after a series of chemotherapies and a bone marrow transplant. The presence of CD 30+ cells led to her excellent response to brentuximab.¹⁶⁻¹⁸ Regrettably, the lymphoma relapsed with massive lymphadenopathy in the mediastinum that caused SVC syndrome. On reviewing the lymphadenopathy in HTLV-1-associated lymphoma, we found the lymphadenopathy was usually characterized as spares the mediastinum,^{9,13,14} except one case report in 1984 that described massive mediastinal adenopathy.¹⁹

Meanwhile, we found massive lymphadenopathy as a presentation of HTLV-1-associated lymphoma, has was not systematically reported in the typical ATL studies.^{5,9} In our systematic review, we found 3 cases of ATL with massive lymphadenopathy.^{7,8} Among the 3 cases, 2 were massive lymphadenopathy within the abdomen, while the other was massive cervical lymphadenopathy (15 cm). All 3 were acute type ATL due to the presence of leukocytosis, hypercalcemia, the elevation of LDH, and bulky lymph node. However, these reported cases lack urgent compression symptoms caused by massive lymphadenopathies, like our cases.

The overall long-term prognosis of patients with ATL has been dismal, ranging between 6 months for the acute subtype and 24 months for the chronic subtype.⁵ Several indicators also predict poor prognosis, for instance, elevated LDH levels, more than 4 involved areas, thrombocytopenia, bone marrow involvement, eosinophilia, hypercalcemia, more than 40 years old, p53 mutation, p16 deletions, high IL-15 serum levels, and C-C chemokine receptor 4 (CCR4) expression.²⁰ The clinical management of ATL mostly depends on the ATL subtype. Cytotoxic combination chemotherapy has been the mainstay of therapy for aggressive type ATL. CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or aggressive combination chemotherapy, VCAP-AMP-VECP (vincristine, cyclophosphamide, doxorubicin, and prednisone; doxorubicin, ranimustine, and prednisone; and vindesine, etoposide, carboplatin, and prednisone), have been the most common choices for patients with chronic, lymphoma, and acute subtypes. However, even with the intensity of chemotherapy, the outcome of aggressive type ATL has remained poor.^{21,22} Recently, monoclonal antibodies have been developed for the management of ATL by targeting the biomarkers. Both our cases were CD30 positive in immunohistochemistry analysis that indicated the chances of good response from brentuximab vedotin as demonstrated in our case 2. Previous retrospective analysis has shown brentuximab vedotin's safety and

efficacy toward adults over 60 years old with relapsed and refractory CD30 positive lymphoma.^{18,23} The promising results of the ECHELON-2 regimen in treating peripheral T-cell lymphoma¹⁶ would encourage us to treat HTLV-1 lymphoma with CD30+ with this regimen, but a clinical trial will be necessary. Moreover, mogamulizumab, an anti-CCR4 antibody, and zidovudine with interferon alfa (AZT/IFN- α), have also had encouraging results in clinical trials toward aggressive type ATL.^{1,24-26}

Conclusion

Here we report 2 cases of HTLV-1-associated lymphoma proven by PCR that presented with massive lymphadenopathy with compression. Clinicians should remain aware of the diagnosis of HTLV-1-associated lymphoma in this presentation, especially when the patients are from endemic areas.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics Approval

Ethics approval to report this case was obtained from Brookdale Hospital IRB Review Board.

Informed Consent

Informed consent for patient information to be published in this article was not obtained because patients expired before we obtained the consent.

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