Human T-cell Lymphotrophic Virus (HTLV-1) and Adult T-Cell Leukemia/Lymphoma (ATL) – Case Report and Literature Review

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BACKGROUND

In the mid-1970s, retroviruses had been discovered in many vertebrate species, including apes. The hypothesis that humans may also be infected with retroviruses led to a search that ultimately resulted in the isolation of a retrovirus from the cell lines and blood of patients with adult T-cell leukemia. This virus is called Human T-cell lymphotropic Virus (HTLV-I). HTLV-I has been linked to a paralytic disease that occurs in the tropics (Caribbean islands) called tropical spastic paraparesis. HTLV-I induced leukemia has also been described in the Caribbean and Japan (1, 2). A second human retrovirus was isolated from T-cells of patients with a T-cell variant of hairy cell leukemia, called HTLV-II, but this virus has no known role in producing disease (3).

Modes of HTLV-I transmission routes are similar to those for HIV and include sexual contact, transfusion of infected blood and blood products, and maternal-child (3). HTLV-I is transmitted from infected women to their offspring predominantly via breast milk, with seroconversion occurring in 18-26% of the breastfed offspring (4–6).

Herein we present a case of a middle aged female of no significant past medical history, with HTLV-I and lymphoma who presented with constitutional symptoms.

Keywords: Human T-cell lymphotrophic virus, leukemia, lymphoma, tropical spastic paresis.

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CASE REPORT

A 55 year old female patient, with no significant past medical/surgical history except for a total hysterectomy (2011) and no known drug and/or food allergies, non-smoker, non-alcoholic, presented to the Emergency Unit with complaints of shortness of breath, difficulty lying flat and abdominal pain for 2 weeks duration. Vitals were temperature 97.2^{o}F, pulse 72/min, respiratory rate 20/min, blood pressure 90/60mmHg and SPO_2 98% on room air. Patient gave a 3-4 week history of "swollen lymph nodes around the neck" for which she saw the district doctor who requested a complete blood count (results: WBC- 87,100mm^3, Hb- 13.4g/dl, HCT- 37%, PLT- 154,000/uL) and ultrasonography which indicated splenomegaly. She received O_2 therapy 5L by face mask, was referred and admitted to the female medical ward.

On physical examination, multiple enlarged firm non-tender lymph nodes were noted around the scalp and both pre-auricular areas, cervical, axillary, and inguinal area. Large tender mass noted to the left lower quadrant (? enlarged spleen), pitting edema to the lower extremities. Patient was alert and oriented to time, person and place, and had good muscle strength to all extremities. Labs done as shown in Table 1 shows a WBC of 84.51 x 10^3/uL on admission. A repeat CBC two days after was 66.6 x 10^3/uL and 137.05 x 10^3/uL on day 5 of hospitalization. Peripheral blood smear reported convoluted nuclei, cleaved nuclei in lymphocytes. Rouleaux 2+

Table 2 shows chemistry results of the patient on admission and one week hospitalization. The result shows lactate dehydrogenase level >1700 U/L and deranged liver enzymes, with an elevated serum uric acid level. Serum BUN and creatinine were within normal limits.

Ultrasonography of abdomen: splenomegaly with dimensions 17.7 x 11.3cm, no focal lesion. The liver, gallbladder, pancrease and both kidneys appear normal. Normal diameter of abdominal aorta, no para-aortic nodes. No free fluid in the peritoneal cavity. No demonstrable abdominal mass at the time.

Mammography: symmetrical parenchymal appearances. A solitary intramammary node is seen in the upper aspect of the left breast – typical of no clinical consequence.

Chest X-Ray: normal cardiac size and configuration. Unremarkable mediastinum. There were bilateral pleural effusions and the presence of a cavitating irregularly contoured lesion in the right lower lobe - ?lung abscess/other pathology.

Sputum for acid fast bacilli - negative

Lymph node biopsy: Histology showed features suggestive of Adult T-cell Lymphoma (See figure 1). Patient was managed with IV fluids, antibiotics, and pain meds.

CT scan of the chest revealed the presence of a small left pleural effusion and parenchymal pulmonary disease in the right lower lobe – consolidation with some focal regions of likely abscess-in-evolution.

Patient was started on levofloxacin 500mg, allopurinol 200mg, hydroxyurea 1g, furosemide 40mg and IV fluids. Discussions were held with the patient and family member regarding patient's status and need for urgent/emergent plasmapheresis, hematology and pulmonologist consultation neither of which is available in St. Vincent and the Grenadines. Arrangements were made and patient was flown to Trinidad.

At Trinidad, patient was assessed and it was indicated that she required five sessions of chemotherapy. She received the CHOP regimen using doxorubicin 70mg, vincristine 2mg, cyclophosphamide 1gm, after pre-medicated with emend (aprepitant ®) 125mg, granisetron 3mg and dexamethasone 12mg. A normal left ventricular function was confirmed with echocardiography before initiating chemotherapy. Patient had minimal complaints post-

therapy, and tolerated the regimen well. Presently, she has received three doses of her chemotherapy and is awaiting the remaining two doses.

DISCUSSION

Painless lymphadenopathy in an adult carries a red flag as this in most cases is seen with chronic inflammation (chronic lymphadenitis), metastatic carcinoma, or lymphoma (7). Since its discovery in the 1970s, studies have elucidated the infection and pathogenesis of HTLV-I. It is known that the virus can be transmitted through sexual contact, from mother to child, and through contaminated blood products. An estimate of 10 to 20 million people is infected worldwide with predominance in Japan, parts of Africa, the Caribbean and South America (8). Early-life exposure to the HTLV-I virus, through mother-to-infant transmission, has been postulated to pose the greatest risk for subsequent development of ATL (9).

Evidence using serological and molecular biological studies showed convincing association of HTLV-I and ATL (10). Other evidence from epidemiological studies confirms the role of HTLV-I in ATL, HTLV- associated myelopathy/tropical spastic paresis (HAM/TSP) and uveitis (11–13). However, a majority of infected people remain asymptomatic; it is not yet fully understood why some infected persons develop associated diseases whereas others do not (14).

There are several types of HTLV-I-induced adult T-cell leukaemia/lymphoma (ATL): acute, lymphomatous, chronic, and smouldering, with a proportion of 55%, 20%, 20% and 5% correspondingly (15). A fifth type of ATL has been described: primary cutaneous tumoral ATL (18). Almost all patients with ATL present with lymphadenopathy and 50% have

hepatosplenomegaly. Skin lesions are also common; they can precede or coincide with the lymphadenopathy and/or splenomegaly. ATL can also affect the lungs, gastrointestinal tract, and central nervous system; involvement of other organs is uncommon (15, 16).

The pathogenesis of HTLV-I-induced ATL stems from the knowledge that it is a malignancy of post-thymic T cells in which the HTLV-I provirus is integrated. Consequently, T-cells are rushed into and through the mitotic phase without checking for chromosomal abnormalities. Escape of checkpoints result in accumulation of genetic damage, and apoptotic cell death does not occur even in cells with severely damaged DNA. In these circumstances, T cells can accumulate DNA mutations, resulting in transformation and monoclonal outgrowth of a truly malignant cell. In addition to these genetic changes, epigenetic changes such as DNA methylation may have an important role in leukaemogenesis (16, 19).

Despite the fact that these phenomena occur in all infected people, only a minority develop ATL. It is possible that the development of ATL is determined mainly by chance, particularly in view of the finding that HTLV infection results in chromosomal instability (20). However, yet unknown factors could be involved in the pathogenesis. This view is supported by the finding that the occurrence of ATL appears to vary according to geographical location (16). In addition, several studies suggest that ATL develops mostly in individuals infected early in life through breastfeeding. Infection of immature thymocytes at young age might increase the risk of later transformation into malignant cells (21). A study of the role of HTLV-I in the development of non-Hodgkin lymphoma in Jamaica and Trinidad and Tobago showed the association is strongest in persons under 40 years old at diagnosis and declined with age, especially among patients with T-cell lymphoma (9). This is consistent with the discussion assuming a latent period of about 20-40 years between childhood exposure and development of a malignant disorder.

The diagnosis of ATL is mainly based on morphological analysis. Peripheral blood smears show pleomorphic atypical lymphoid cells with basophilic cytoplasm and convoluted nuclei, described as “flower cells”. The integrated HTLV-I provirus can be detected in these cells (22). During the leukemic phase, the WBC count may increase to hundreds of thousands. The predominant immunologic phenotype of malignant cells is helper T cell, CD3+, CD4+, L-selectin+, CD25+, CD45RA+, HLA-DR+, CD29–, and CD45RO– in peripheral blood, or CD3+, CD4+, L-selectin+, CD29+, CD45RO+, HLA-DR+, and CD45RA– in the skin and lymph nodes (22). High expression of Ki67 antigen is associated with a poor prognosis. A parathyroid hormone-related peptide is frequently increased in ATL patients, and could result in hypercalcemia (23). This, as well as lactate dehydrogenase, soluble IL-2 receptor, neuron-specific enolase, thymidine kinase, and β_2-microglobulin are all associated with a poor prognosis (22).

Many strategies have been evaluated for the treatment of ATL, and the following therapies appear to improve the prognosis compared with conventional chemotherapy: interferon-α with zidovudine, intensive chemotherapy plus granulocyte colony-stimulating factor support, and allogenic haematopoietic stem cell transplantation (19, 23). The rationale for therapy with CHOP can be explained by the reduction in tumor burden. An improvement in survival is achieved when antiretroviral therapy and oral etoposide was used following treatment with CHOP, IFN-α, and an antinucleoside (zidovudine or zalcitabine) (25). Nevertheless, the median survival of patients with acute, lymphomatous, and progressing chronic ATL remained low: less than 18 months in most reports (19, 24). Novel approaches include histone deacetylation inhibitors, monoclonal antibodies, and proteasome inhibitors, but their added value remains to be established (19).

CONCLUSION

The spectrum of manifestations of HTLV infection remains broad and diagnosis is frequently delayed as it can range from an asymptomatic patient to one with generalized non-tender lymphadenopathy as seen in our case. Early diagnosis, especially in pregnant women can help reduce the incidence of HTLV infection and ATL, which develops decades after. Although ATL is an aggressive neoplasia with a poor prognosis, successful treatment has been reported. The presence of Ki67 antigen, increased LDH, serum calcium, soluble IL-2 receptor, neuron-specific enolase, thymidine kinase and β_2-microglobulin are associated with poor prognosis. Further studies on arresting the transformation of infected T-cells, and/or interrupting mother-to-infant transmission where breastfeeding is unavoidable would be a better approach in preventing HTLV-associated ATL.

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Table 1: Comparison of hematology labs on admission and one week during hospitalization

Tests	On admission	One-week Hospitalization	Units	Normal range
WBC	84.51	134.70	10^3/Ul	4.00 – 10.00
RBC	4.02	4.12	10^6/Ul	4.10 – 5.40
HBG	13.4	12.0	g/Dl	12.0 – 18.0
HCT	36.3	34.7	%	38.0 – 47.0
MCV	77.1	84.2	fL	76.0 – 100.0
MCH	28.5	29.1	pg	26.0 – 38.0
MCHC	36.9	34.6	g/dL	31.0 – 37.0
PLATELETS	146	41	10^3/uL	150 – 450
RDW-CV	19.9	19.4	%	11.0 – 16.0
MPV	11.2	8.2	fL	9.0 – 13.0

Table 2: Comparison of chemistry labs on admission and one week during hospitalization

Tests	On admission	One-week Hospitalization	Units	Normal range
SODIUM	140	138	mmol/L	136 - 145
POTASSIUM	3.8	2.8	mmol/L	3.5 – 5.1
CHLORIDE	102	101	mmol/L	98 - 107
CO_2	18	21	mmol/L	22 - 29
UREA	3.5	5.8	mmol/L	2.5 – 7.5
CREATININE	75	116	umol/L	50 - 140
eGFR	84.1	51.0	mL/min	>60
TOTAL PROTEIN	68	55	g/L	64 - 83
ALBUMIN	38	30	g/L	35 - 52
GLOBULIN	30	25	g/L	20 – 48
A/G RATIO	1.3	1.2	Ratio	0.6 – 2.2
AST	85	109	U/L	5 – 34
LDH	1798	1729	U/L	125 – 220
ALKALINE PHOSPHATASE	247	316	U/L	39 – 130
ALT	23	24	U/L	0 – 55
GGT	272	443	U/L	8 – 40
TOTAL BILIRUBIN	47	62	umol/L	3.4 - 22
URIC ACID		0.55	umol/L	

Table 3: Serology workup

Tests	Result
VDRL	Non-Reactive
TPHA	Reactive
HEPATITIS A ANTIBODY	Non-Reactive
HEPATRITIS B SURFACE ANTIGEN	Non-Reactive
HEPATITIS C ANTIBODY	Non-Reactive
HIV I/II	Non-Reactive
HTLV	Reactive

VDRL-Veneral Disease Research Laboratory, TPHA-Treponema pallidium Hemagluttination Assay, HIV-Human Immunodeficiency Virus, HTLV-Human T-cell Leukemic/Lymphotropic Virus.

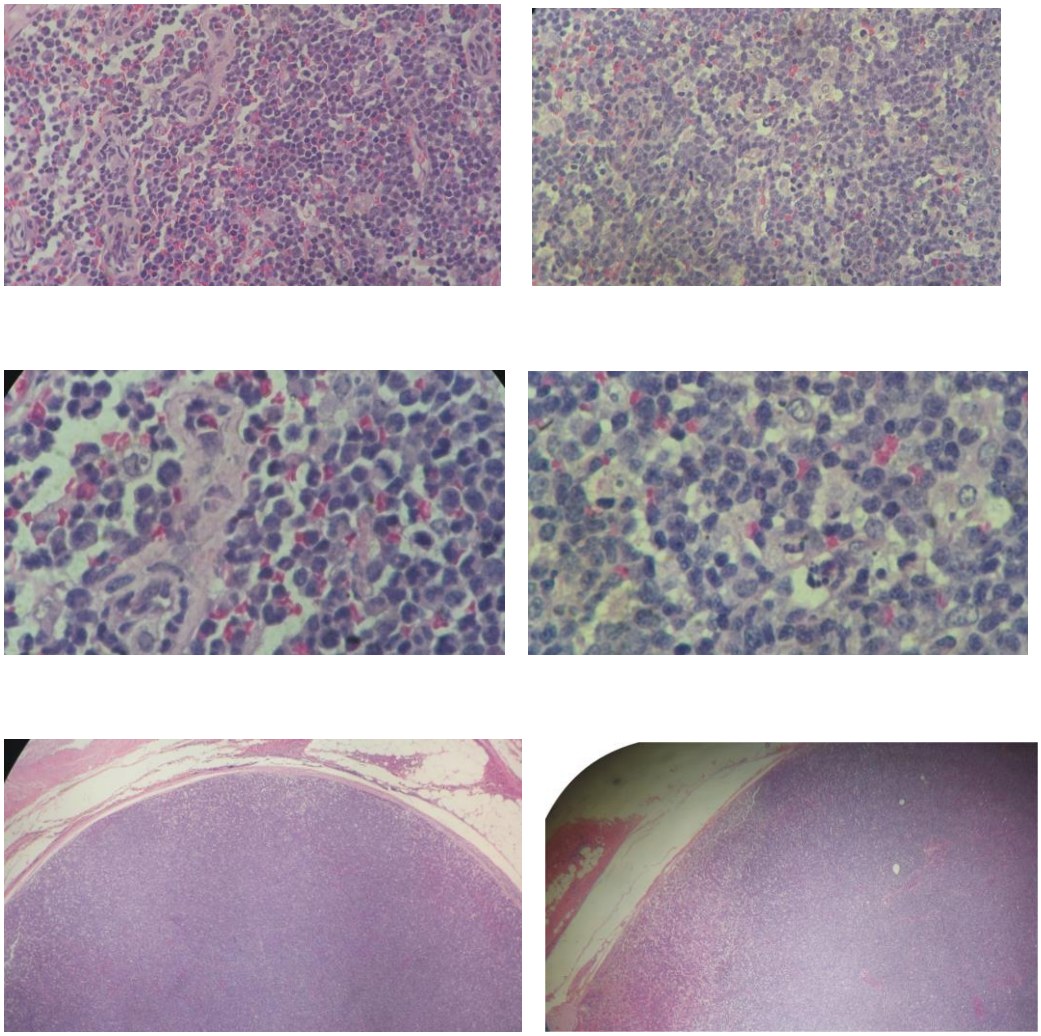

Figure: H&E sections from a cervical lymph node of the patient, showing large lymphoid cells. Pleomorphic cells with nuclear irregularities. Slides of different magnifications showing anaplastic large cells with abundant, eosinophilic cytoplasm and intact capsule.