CASE REPORT

Human T-cell Lymphotropic Virus and Adult T-cell Leukaemia/Lymphoma: Case Report and Literature Review

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ABSTRACT

HTLV-I is the first retrovirus directly associated with human malignancy. HTLV-I is endemic in the Caribbean, Japan, parts of Africa, the Middle East and South America. This enveloped double-stranded RNA virus is transmitted by routes similar to HIV, including untested blood/blood product transfusions, sexual contact, intravenous drug abuse, and from mother to child in a vertical transmission. HTLV infection rarely occurs outside of the above sites and very few studies are available globally. Although the retrovirus identified as being associated with chicken sarcoma was described by Rous (1908), the first human retrovirus was not isolated until 1978 from cutaneous T-cell lymphoma in black Americans. Endemicity of the disease in the Caribbean was discovered in 1982 after adult T-cell leukemia (ATL) was found in some London patients, all of Caribbean origin. To date, there is still a lack of studies on the role of viruses in diseases such as inflammatory disorders, arthritis, Sjogren's syndrome, and infectious dermatitis. In Saint Vincent, there were no documented studies that reflected the prevalence and expression of the virus although we did report some cases of HIV-positive HTLV-I ATL. This article discusses the diagnosis and management of a 55-year-old female with an atypical presentation of adult T-cell lymphoma, and we conducted a literature review to determine the prevalence and common presentations of ATL.

Keywords: Human T-cell lymphotropic virus, leukaemia, lymphoma, tropical spastic paresis.

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 leukaemia. This virus is called human T-cell lymphotropic virus (HTLV-I). It has been linked to a paralytic disease that occurs in the tropics (Caribbean islands) called tropical spastic paraparesis. The HTLV-I-induced leukaemia 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 leukaemia, 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). Transmission of HTLV-I is mainly 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 with no significant past medical history, with HTLV-I and lymphoma, and who presented with constitutional symptoms.

CASE REPORT

A 55-year-old female patient, with no significant past medical/surgical history except for a total

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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 of duration. Vital signs were temperature 97.2°F, pulse 72/minutes, respiratory rate 20/minutes, blood pressure 90/60 mmHg, and SPO2 98% on room air. Patient gave a 3- to 4-week history of 'swollen lymph nodes around the neck' for which she saw the district doctor who requested a complete blood count (CBC) (results: white blood cell count [WBC], 87 100 mm^3; haemoglobin, 13.4 g/dL, haematocrit, 37%, platelet, 154 000/µL) and ultrasonography which indicated splenomegaly. She received O2 therapy 5 L by face mask, and 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 and cervical, axillary and inguinal areas. Large tender mass noted to the left lower quadrant (suspicious of an enlarged spleen), with pitting oedema to the lower extremities. The patient was alert and oriented to time, person and place, and had good muscle strength to all extremities. Laboratory tests done as shown in Table 1 show a WBC of 84.51 × 10^3/µL on admission. A repeat CBC 2 days after was 66.6 × 10^3/µL and 137.05 × 10^3/µL on day 5 of hospitalization. Peripheral blood smears showed convoluted cleaved nuclei in lymphocytes and 2+ Rouleaux formation.

Table 1: Comparison of haematology labs on admission and 1 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/µL	150–450
RDW-CV	19.9	19.4	%	11.0–16.0
MPV	11.2	8.2	fL	9.0–13.0

WBC = white blood cell; RBC = red blood cell; HBG = haemoglobin; HCT = haematocrit; MCV = mean corpuscular volume; MCHC = mean corpuscular haemoglobin concentration; RDW-CV = red cell distribution width co-efficient of variation; MPV = mean platelet volume.

Table 2 shows chemistry results of the patient on admission and 1 week after hospitalization. The result shows lactate dehydrogenase (LDH) level >1700 U/L and deranged liver enzymes, with an elevated serum uric acid level. Serum blood urea nitrogen and creatinine were within normal limits.

Table 2: Comparison of chemistry labs on admission and 1 week during hospitalization

Tests	On admission	One-week hospitalization	Units	Reference 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	µmol/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	µmol/L	3.4–22
Uric acid	–	0.55	mmol/L	0.18–0.48

eGFR = estimated glomerular filtration rate; AST = aspartate aminotransferase; LDH = lactate dehydrogenase; ALT = alanine transaminase; GGT = gamma-glutamyl transpeptidase.

Ultrasonography of the abdomen showed splenomegaly with dimensions 17.7 × 11.3 cm and no focal lesion. The liver, gallbladder, pancreas and both kidneys appear normal. The abdominal aortic diameter was normal, and there were no para-aortic lymph nodes. No free fluid in the peritoneal cavity. No demonstrable abdominal mass at the time.

Mammography showed 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 showed normal cardiac size and configuration, and unremarkable mediastinum. There were bilateral pleural effusions and the presence of a cavitating irregularly contoured lesion in the right lower lobe—suspicious for lung abscess or other lung pathologies. Sputum for acid fast bacilli is negative.

Lymph node biopsy showed histological features suggestive of adult T-cell lymphoma (Figure). The patient was managed with IV fluids, antibiotics and pain meds.

Computed tomography scan of the chest revealed the presence of a small left pleural effusion and parenchymal

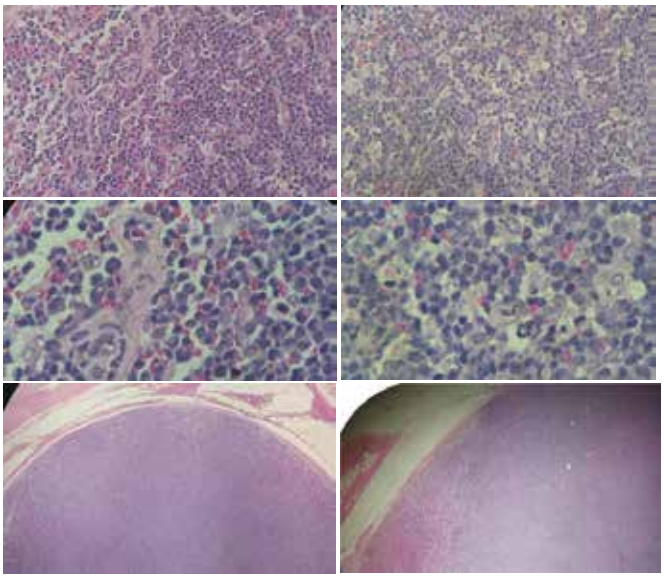

Figure: H&E sections from a cervical lymph node of the patient, showing large lymphoid cells. Pleomorphic cells with nuclear irregularities. Slides of different magnifications showing anaplastic large cells with abundant eosinophilic cytoplasm and intact capsule.

pulmonary disease in the right lower lobe—consolidation with some focal regions of likely abscess in evolution.

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

At Trinidad, the patient was assessed, and it was indicated that she required five sessions of chemotherapy. She received the CHOP regimen using doxorubicin 70 mg, vincristine 2 mg, cyclophosphamide 1 g, after pre-medicated with emend (Aprepitant®) 125 mg, granisetron 3 mg, and dexamethasone 12 mg. A normal left ventricular function was confirmed with echocardiography before initiating chemotherapy. The 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 are 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) (Table 3). Other evidence from epidemiological studies confirms the role of HTLV-I in ATL, HTLV-associated myelopathy/tropical spastic paresis 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).

Table 3: Serology workup

Tests	Result
VDRL	Non-reactive
TPHA	Reactive
Hepatitis A antibody	Non-reactive
Hepatitis B surface antigen	Non-reactive
Hepatitis C antibody	Non-reactive
HIV I/II	Non-reactive
HTLV	Reactive

VDRL = Veneral Disease Research Laboratory; TPHA = *Treponema pallidum* haemagluttination assay, HIV = human immunodeficiency virus; HTLV = human T-cell leukaemic/lymphotropic virus.

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%, respectively (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 lymphadenopathy and/or splenomegaly. Adult T-cell leukaemia/lymphoma 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 (17). Consequently, T-cells are rushed into and through the mitotic phase without checking for chromosomal abnormalities. Escape of checkpoints results 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 leukemogenesis (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, 25). During the leukaemic 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 hypercalcaemia (23, 25). This, as well as LDH, soluble IL-2 receptor, neuron-specific enolase, thymidine kinase, and β2-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 (IFN-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 tumour burden. An improvement in survival is achieved when antiretroviral therapy and oral etoposide were used following treatment with CHOP, IFN-α and an antinucleoside (zidovudine or zalcitabine) (26). Nevertheless, the median survival of patients with acute, lymphomatous and progressing chronic ATL remained low: less than 18 months in most reports (19, 24, 26). 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 β2-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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