Human T-Cell Lymphotropic Virus

Christine Dueck, MD; and John M. Embil, MD, FRCPC

The family of human T-cell lymphotropic viruses (HTLVs) consists of those with infective affinity for humans. HTLVs are enveloped RNA retroviruses characterized by an ability to stimulate T-cell proliferation and establish persistent infection and therefore, are this month's **Bug of the Month**.

What is HTLV-1?

There are four subtypes of HTLVs, of which HTLV-1 is the best known and the only subtype clearly linked to lymphoproliferative disease. HTLV-2 is found globally and is the most common HTLV infection in injection drug users (IDUs). It is associated with hairy cell leukemia and myelopathy. HTLV-3 and -4 exist in limited populations and have unknown clinical significance. Given its ubiquity and its impact on morbidity, HTLV-1, specifically its two most serious manifestations, will receive the focus in this article.

HTLV-1 was the first isolated human retrovirus and the first to be associated with malignancy.

HTLV-1 was the first isolated human retrovirus and the first to be associated with malignancy.

HTLV-1 is involved in the pathogenesis of the following conditions:

- Adult T-cell leukemia/lymphoma (ATL)
- HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP)
- Infective dermatitis in children
- HTLV-1-associated uveitis
- Various rheumatological diseases, including Sjögren's syndrome and polymyositis
- HIV co-infection which accelerates the progression of AIDS

Who acquires HTLV-1?

HTLV-1 infection is endemic to:

- West Africa,
- Japan,
- the Caribbean,
- parts of North and South America and
- Melanesia.

Seroprevalence ranges from 3% to 6% in the Caribbean islands, to 30% in southern Japan and 0.001% to 0.03% in blood donors in Europe. The geographic trend declines with the migration of carriers to non-endemic areas.

Prevalence increases with age and is twice as high in women; the gender difference emerges at 20- to 30-years-of-age, with sexual activity.

There is a 5% lifetime risk of developing HTLV-1.

How is HTLV-1 transmitted?

There is a 5% lifetime risk of developing HTLV-1. Transfusion of HTLV-1 occurs in whole blood and packed red cells and is the most efficient mode of viral transmission. The probability of infection by transfusion is 40% to 60%; secondary HAM/TSP and ATL have been reported. In the US, HTLV-1 has been identified primarily in IDUs and in their families. For healthcare workers, the risk for occupational transmission of HTLV-1 is less than for the Hepatitis B virus and equal to or less than that of HIV. Mother-to-child transmission is the second most common means of virus transfer, occurring at a rate of 18% to 38%. Breastfeeding for more than six months may be the most important

means by which infants are infected. Sexual transmission of HTLV-1 exists, although it is significantly less efficient than for HIV. The male-to-female transmission occurs at a ratio of 4:1.

Mother-to-child transmission is the second most common means of virus transfer, occurring at a rate of 18% to 38%.

What is ATL?

ATL is a mature T-cell non-Hodgkin lymphoma, most common in men, with a leukemic phase characterized by circulating, activated CD4+/CD25+ T-cells. HTLV-1 provirus is integrated into the host genome of malignant cells. The average age of onset is 58 years and illness develops after an incubation period of 20 to 30 years. Diagnostic criteria for ATL include:

- HTLV-1 seropositivity,
- abnormal lymphocytes with cleaved, convoluted nuclei ("flower cells"),
- histology and/or cytology of malignant T-cells and
- serum lactate dehydrogenase (LDH) activity.

ATL is diagnosed serologically by an enzyme-linked immunosorbent assay (ELISA), which will detect antibodies directed against specific HTLV antigen. Cases detected by ELISA require confirmation, typically by Western blot. ATL is classified as acute, chronic, lymphomatous, or smouldering ATL; differences are outlined in Table 1. Thirty-nine per cent of ATL cases have widespread or localized skin lesions at diagnosis. Lymphadenopathy, hepatosplenomegaly and hypercalcemia are common, as is leukocytosis (with neutrophil and eosinophil predominance). Immune suppression manifests as bacterial and opportunistic infections which contribute to a poor prognosis.

Table 1

Subtypes of adult T-cell leukemia (ATL)/lymphoma

Presentation	ATL subtype			
	Acute ATL	Smouldering ATL	Chronic ATL	Lymphomatous ATL
Prodome	short and aggressive			
Lytic bone lesions	+	–	–	–
Cutaneous lesions	+	+	±	+[3]
Hepatosplenomegaly	+	–	±	–
Pulmonary involvement	+	±	–	–
Lymphadenopathy	±	–	±	+
Hypercalcemia	+	–	–	–
Lymphocytosis	+	+[1]	+[2]	–
↑ Lactate dehydrogenase	–	+	++	–

+: present –: absent ±: may or may not be present ++: more present ↑: elevated

1. Abnormal T-cells of ≤ 3%, malignant cells with monoclonal proviral integration
2. Abnormal T-cells ≥ 3.5 x 10^9/L, absolute lymphocytosis ≥ 4.0 x 10^9/L
3. Histologic evidence of lymph node involvement necessary

Intensified chemotherapy for non-Hodgkin lymphoma can prolong life in ATL, but is not considered curative. The median survival for ATL is less than one year, with death usually from overwhelming infection or hypercalcemia.

What is HAM/TSP?

HAM/TSP causes an upper motor neuron syndrome with inflammation, demyelination and necrosis of the spinal cord. Patients present with urinary incontinence, impotence and radiculopathy. Pathogenesis is thought to involve a direct effect of cytotoxic T-cells on infected glial cells and a T-cell immune response invoked by HTLV-1.

The average age of diagnosis is 40 years, commonly preceded by adult-acquired infection. The lifetime risk of developing HAM/TSP among carriers of HTLV-1 is an estimated 2%, lower than that of ATL. In contrast to ATL, HAM/TSP is more common in women than in men.

Laboratory features of HAM/TSP include high titres of anti-HTLV-1 antibodies in serum and cerebrospinal fluid, as well as "flower" lymphocytes in half of affected patients. A MRI of the spinal cord may reveal atrophy while brain imaging shows white matter degeneration similar to multiple sclerosis, findings that correlate with age > 50 years. Patients acquiring HTLV-1 by transfusion progress faster to paralysis. It is unclear why some HTLV-1 carriers develop disease and why ATL develops in some and HAM/TSP in others.

A vaccine for HTLV-1 is in development; given the strong cross-reactivity between human immune sera and viruses from endemic areas, a vaccine should be protective.

HAM/TSP is progressively disabling and its complications may cause death after many years. Initially, the virus can be tempered with systemic or intrathecal corticosteroids but no treatment for advanced infection has been found.

What are the global implications of HTLV-1 infection?

A vaccine for HTLV-1 is in development; given the strong cross-reactivity between human immune sera and viruses from endemic areas, a vaccine should be protective.

Current prognosis for HTLV-related disease is poor and the course may only be tempered with non-specific measures. Efforts, then, should focus on reducing transmission of HTLV-1, particularly via needle use and breastfeeding, which should decrease the incidence of related malignancies and neuropathies. Particular attention should be turned to public health measures in endemic regions, although implementing these strategies poses challenges in less-developed nations.

cme

Dr. Dueck is a Resident in Pediatrics, University of Manitoba, Winnipeg, Manitoba.

Dr. Embil is a Consultant, Infectious Diseases and an Associate Professor, University of Manitoba. He is also the Medical Director, Infection Prevention and Control Program, Health Sciences Centre and Winnipeg Regional Health Authority, Winnipeg, Manitoba.