TEACHING CASE REPORT

Human T-cell lymphotropic virus type 1-associated adult T-cell leukemia/lymphoma in the Inuit people of Nunavut

DOI:10.1503/cmaj.060242

Case 1: A 55-year-old Inuit woman from Nunavut presented with a 2-week history of malaise, pain in the right upper abdominal quadrant and mild jaundice. She had a history of tuberculosis, *Helicobacter pylori* gastritis and peptic ulcer disease. Complete blood count (CBC) results showed a leukocyte count of 79×10^9/L, with 90% lymphocytes and many "flower cells." Flow cytometry immunophenotyping of the peripheral blood lymphocytes was compatible with adult T-cell leukemia/lymphoma (ATLL), with positivity for CD2, CD3, CD4, CD5 and CD25, and aberrant loss of CD7. The diagnosis was confirmed with positivity for anti-HTLV-1 (human T-cell lymphotropic virus type 1) antibodies. DNA polymerase chain reaction (PCR) and sequencing analysis of the complete long-terminal repeat region and envelope glycoproteins gp46 and gp21 of the peripheral blood mononuclear cells confirmed the presence of HTLV-1 of the "transcontinental" subgroup A of the Cosmopolitan clade a. Chemotherapy and antiviral therapy were administered, with minimal response. The patient died 3 months after presentation.

Case 2: A 44-year-old Inuit woman from Nunavut presented with a nonspecific eczematous follicular dermatitis. Skin biopsy showed a dermal infiltrate of atypical lymphocytes with epidermotropism and Pautrier microabscesses (Fig. 1), which suggested plaque stage mycosis fungoides. A decreased level of consciousness subsequently developed. The patient's serum calcium level was elevated (3.52 mmol/L), as were the liver enzyme and serum creatinine levels. Leukocytosis was noted, with a leukocyte count of 182×10^9/L, with 82% leukemic lymphoid cells and "flower cell" morphology (Fig. 2). Flow cytometry immunophenotyping of these lymphocytes was compatible with ATLL, and results of testing for anti-HTLV-1 antibodies were positive. The patient was given chemotherapy and antiviral therapy, with poor response, and died.

Case 3: A 68-year-old Inuit woman from Nunavut presented with fever and shortness of breath. She had hypercalcemia, elevated liver enzyme levels and a peripheral blood leukocyte count of 21×10^9/L, with CD4+ T-cell lymphocytes, including "flower cells." DNA PCR and sequencing analysis demonstrated the presence of HTLV-1 virus of the "transcontinental" subgroup A of the Cosmopolitan clade a, similar to case 1. The patient had a history of chronic obstructive pulmonary disease, congestive heart failure and a recent episode of *Clostridium difficile* enteritis. A few months earlier, biopsy of a skin lesion had shown Kaposi's sar-

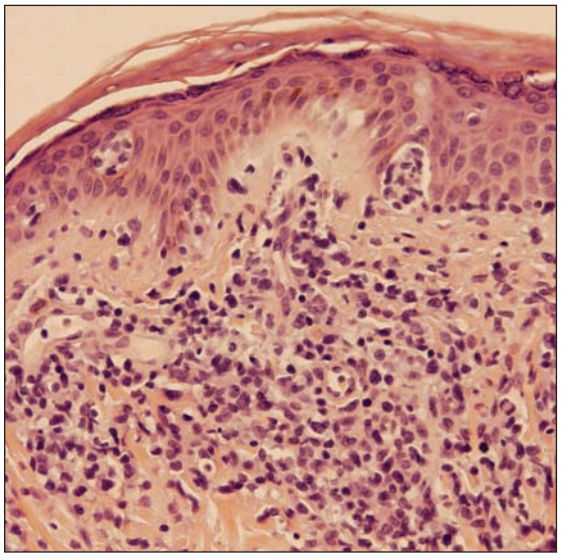

Fig. 1: Skin biopsy (left arm) showing dermal infiltrate of atypical lymphocytes with epidermotropism. Nests of atypical lymphocytes are visible in the epidermis, compatible with Pautrier microabscesses (hematoxylin and eosin stain, original magnification × 20).

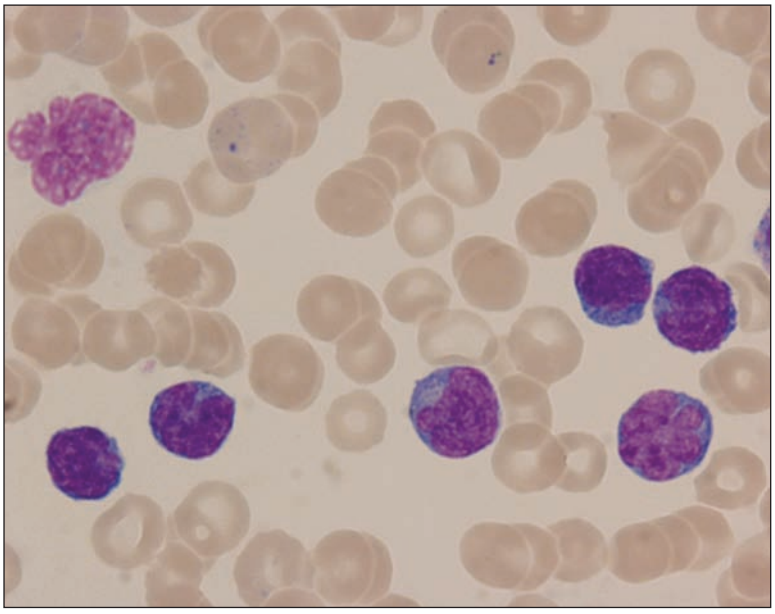

Fig. 2: Peripheral blood lymphocytosis. Note typical "flower cell" (lower right) and smudge cell (upper left) (Wright–Giemsa stain, original magnification × 100).

coma. Serologic testing for HIV yielded negative results. A palliative treatment plan was started, and the patient subsequently died.

ATLL is associated with the human retrovirus HTLV-1, with clonal integration of the HTLV-1 virus in the T cells.[1] Nonviral causes of ATLL are not part of the World Health Organization definition of this disorder and may result from failure to serologically detect anti-HTLV-1 antibodies. Box 1 summarizes the key clinical characteristics of ATLL. ATLL is subclassified into 4 groups: acute, lymphomatous, chronic and smouldering. The acute form typically involves multiple organs (including the central nervous system), the skin, a leukemic peripheral blood picture, hepatosplenomegaly and systemic lymphadenopathy. Lytic bone lesions are often present with hypercalcemia. The peripheral blood leukemic cells are multilobated lymphocyte "flower cells," with a T-helper cell immunophenotype and expression of CD2, CD3, CD4, CD5 but not CD8. CD7 expression is often lost. The strong expression of CD25 (interleukin-2 receptor) is characteristic of ATLL and helps to distinguish this disorder from cutaneous T-cell lymphoma. Acute ATLL is an aggressive disease, with a median survival time of 6 months. Patients with acute ATLL are immunocompromised and at risk of disseminated disease with *Strongyloides*; therefore, investigation for *Strongyloides stercoralis* should be part of the routine work-up in cases of the more aggressive forms of ATLL. The lymphomatous type of ATLL is dominated by generalized lymphadenopathy, without peripheral blood involvement. Hepatosplenomegaly and hypercalcemia are observed. The clinical course is aggressive, with a median survival time of 10 months. The chronic and smouldering forms of ATLL are associated with prolonged survival, with more than 10% and less than 5% circulating leukemic cells, respectively.

Box 1: Key clinical characteristics of adult T-cell leukemia/lymphoma[1]

Acute (50% of cases)

- Leukocytosis of CD4+ T-cells with "flower-like" morphology
- Skin lesions
- Lytic bone lesions, hypercalcemia, elevated lactate dehydrogenase (LD) level
- Opportunistic infections
- Aggressive clinical course, median survival 6 months

Lymphomatous (25% of cases)

- Generalized lymphadenopathy, without peripheral blood involvement
- Hepatosplenomegaly, hypercalcemia, elevated LD level
- Aggressive clinical course, median survival 10 months

Chronic (20% of cases)

- Leukocytosis, with > 10% circulating leukemic cells
- Other clinical features are mild (mild lymphadenopathy, mild hepatosplenomegaly, variable rash, slightly elevated LD level)
- Normal serum calcium level
- Median survival > 2 years

Smouldering (5% of cases)

- Normal leukocyte count, with < 5% circulating leukemic cells
- Skin and pulmonary lesions may be present
- Other clinical features absent (no lymphadenopathy, no hepatosplenomegaly, normal LD level, normal serum calcium level)
- Median survival > 5 years

Transmission of HTLV-1 may be horizontal (through transfusion of cellular blood products, sexual intercourse or sharing of contaminated needles) or vertical (transplacental, intrapartum or through breast-feeding). The clinical manifestations of acute infection with HTLV-1 are not well documented, but they may be asymptomatic or similar to a mild, flu-like illness. In the natural history of this infection, the majority of people infected with HTLV-1 do not go on to experience clinically significant complications. ATLL develops in about 1% to 4% of these people, with a latency of 20 to 30 years, and HTLV-1–associated myelopathy/tropical spastic paresis (HAM/TSP) develops in 0.1% to 1%, with a slightly shorter latency period. Other clinical syndromes associated with HTLV-1 include arthropathy, uveitis, infectious dermatitis in children and Sjögren's syndrome.

HTLV-1 infection is endemic in the Caribbean, southwestern Japan (especially the island of Kyushu), parts of Central and South America, central Asia, the Middle East, Melanesia and sub-Saharan Africa (Fig. 3).[1] Infection with the HTLV-1 virus has also been reported in circumpolar populations, including Aboriginal people in Alaska, the Lapps of Sweden, the Nivkhi of Eastern Russia and, most recently, the Inuit people of Nunavut.[2] In cases where HTLV-1 strains in these populations have been

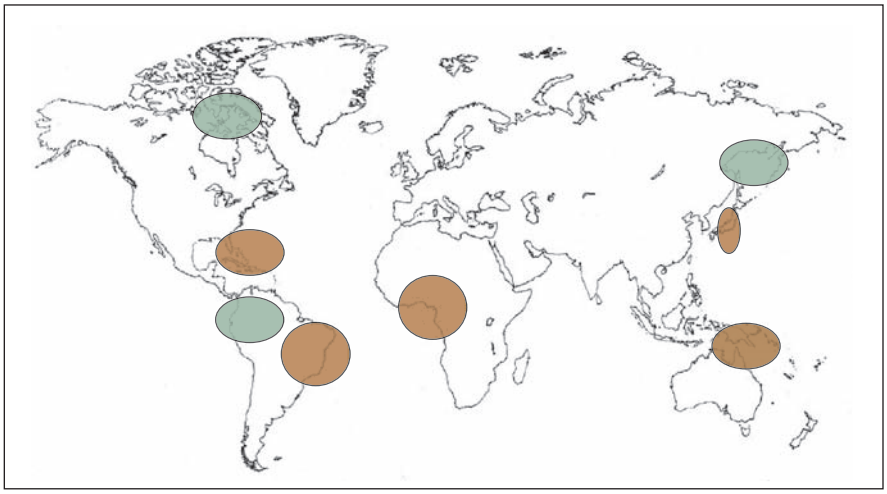

Fig. 3: Regions of endemic human T-cell lymphotropic virus type 1 (HTLV-1) infection (brown regions). Populations of proposed common ancestry (where HTLV-1 virus of the Cosmopolitan clade a, transcontinental subgroup A, has been identified) (green regions).

examined genetically to determine their phylogenetic affinities (including the present cases), they have been shown to belong to a large, globally distributed genealogic cluster termed "Cosmopolitan subclade A." This could reflect the relatively recent common ancestry of circumpolar peoples.[3]

Treatment with combined chemotherapy used to treat non-Hodgkin's lymphoma is usually ineffective in cases of acute ATLL. Antiviral medications, including α-interferon and zidovudine, are useful, but the response is usually transient. Follow-up of asymptomatic patients infected with HTLV-1 is warranted. Recommendations for clinical and laboratory follow-up are summarized in Box 2. These may be performed every 6 months and are designed to elicit the earliest manifestations of ATLL or HAM/TSP. DNA testing to assess proviral load, clonal integration of the viral genome and antigenic drift may also provide additional information concerning the risk of clinically significant syndromes. A first step in the prevention of ATLL is testing for HTLV-1 antibodies in endemic areas. Measures may then be directed to limit the impact of HTLV-1 infection. Breast-feeding for less than 7 months has been shown to reduce the prevalence of infection to the same level as that among infants who are not breast-fed at all. Mothers infected with HTLV-1 who shorten the duration of breast-feeding to the first 6 months of life may limit vertical transmission while retaining the overall benefits of breast-feeding. The likelihood of transmission of HTLV-1 to the baby is also reduced by freezing and rethawing breast milk. Transmission through sexual intercourse is mostly male to female, and the use of condoms may decrease the risk. In the future, there may be a role for antiretroviral agents and monoclonal antibody therapy (alemtuzumab) in reducing the proviral load in HTLV-1 carriers. High proviral load has been linked to an increased risk of transmission to others and an increased risk of HAM/TSP and ATLL. Preliminary findings of studies suggest that the Tax transactivator viral protein may be a suitable target for vaccination development.

Box 2: Proposed guidelines for clinical follow-up of HTLV-1–seropositive individuals in Nunavut

Clinical exam with family physician every 6–12 months

This should include a history and physical exam directed to detect findings suggestive of early blood malignancy of adult T-cell leukemia/lymphoma (ATLL) or the neurologic sequelae of HTLV-1–associated myelopathy, or both.

The history is directed to reveal:

- any urinary incontinence or proximal muscle weakness of the lower extremities
- a change in chronic rash (e.g., now resistant to usual treatment) or the onset of a new rash as described below
- new onset of bone pain, or newly noticed enlarged lymph nodes
- new onset of persistent diarrhea

The physical exam should include:

- testing of proximal muscle strength and observation of gait
- testing of patellar deep tendon reflexes to assess for hyper-reflexia
- palpation for lymphadenopathy
- noting new or changed skin conditions (e.g., rash showing papular/nodular or plaque-like lesions, or infective dermatitis in children)

Discussion of risk factors for transmission of the virus, including breast-feeding, as well as contact tracing and testing of sexual partners can be reviewed at periodic visits with individuals in appropriate risk groups. (All seropositive cases need to be brought to the attention of the chief medical officer of health.) Any psychological concerns of the patient with HTLV-1 infection and possible future health issues may be addressed and assessed for any further consultation with local mental health workers and counsellors as needed.

Investigations

- complete blood count (CBC) and serum calcium measurement every 6–12 months with the above clinical follow-up
- peripheral blood flow cytometry should be added to the laboratory work on an annual basis after age 40
- collection of stools for *Clostridium difficile* for any persistent diarrheal illness
- biopsy of suspicious skin lesions

On interim visits to the community health centre, community health nurses may note or examine any of these symptoms or physical findings and assess the need to do CBC and serum calcium measurement before the next visit, in consultation with the community physician.

Note: HTLV-1 = human T-cell lymphotropic virus type 1.

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Competing interests: None declared.

Acknowledgement: We thank Dr. Joe Hildes of Nunavut for generously sharing the proposed guidelines for clinical follow-up of HTLV-1–seropositive individuals in Nunavut.

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