

HTLV-1 Associated Adult T-cell Leukemia/Lymphoma in Israel: report of two patients of Romanian origin

Haematologica 2005; 90(4):e36-e38

Human T-lymphotropic virus type 1 (HTLV-1) was the first human oncovirus isolated by Gallo et al in 1980¹ and established as an etiological agent for adult T-cell leukemia/lymphoma (ATL).² Although more than 15 million individuals are infected by HTLV-1 through the world, the spread of the virus is highly endemic. The HTLV-1 infection is prevailing in southwestern Japan, inter-tropical Africa, Central and South America.³ In Kyushu district, Japan, the seroprevalence reaches >30% in the adult population. In the US, Europe and the Middle East the HTLV-1 infection is very rare, and cases of ATL have been reported sporadically. We describe here acute ATL in two patients of Jewish-Romanian origin. The epidemiological anamnesis and screening indicate that both patients acquired the HTLV-1 from their mothers leaving in Romania.

Case reports

Case 1. A 49-year-old woman who was born in Romania and immigrated to Israel at age of 9 years, presented in April 2001 with a 2-months history of fever, weight loss, night sweats and back pain. She denied intravenous drug abuse, blood transfusion or travel outside Israel. Physical examination revealed marked splenomegaly and mild cervical and axillary lymphadenopathy. Blood tests showed leukocytosis $15 \times 10^9/L$ with 60% lymphocytes. Peripheral blood smear revealed numerous lymphocytes, part of them showing irregular, convoluted and polylobated nuclei, some resembling flower shape. The lymphocytes demonstrated the phenotype: CD3 60%, CD4 83%, CD25 54%. Bone marrow biopsy disclosed interstitial and focal infiltrate composed by medium-sized lymphocytes with irregular nuclei. Karyotype was 46,XX. Cervical lymph node biopsy demonstrated diffuse infiltrate by lymphoma cells positive for CD3 and CD4. Serum calcium was markedly elevated 19.4 mg/dL (normal 8.5-10.2), lactic dehydrogenase (LDH) was 521 u/L (normal 120-380), phosphorus, liver transaminases and parathyroid hormone were normal. Radiographic survey revealed multiple osteolytic lesions of the skull. Antibodies against HTLV-1 were detected by enzyme linked immunosorbent assay (ELISA). Western blot (INNO-LIA HTLV I/II, Innogenetics, Ghent, Belgium) showed reactivity to two *gag* (p19-I, p24) and two *env* (gp46-I, gp21) antigens of HTLV-1 corresponding to the Cosmopolitan type. Diagnosis of ATL associated with HTLV-1, was established. In addition, antibodies reactive to hepatitis C virus (HCV) were detected by serological screening, and the presence of viral RNA was confirmed by polymerase chain reaction (PCR).

Serological testing of family members revealed that her mother was seropositive for HTLV-1 but seronegative for HCV. One of her two sons was seronegative for both HTLV-1 and HCV, and her second son and husband refused to undergo testing.

The chemotherapy according to the ProMACE-CytaBOM regimen (prednisone, adriamycin, cyclophosphamide, etoposide, cytarabine, bleomycin, oncovin, methotrexate) was started with addition of lamivudine and pamidronate. Partial remission was achieved following two cycles with resolution of symptoms and normal-

ization of laboratory tests. Treatment course was complicated by recurrent episodes of chemotherapy-induced neutropenia and infection, including *Corynebacterium* sepsis, which were successfully treated with colony stimulating factor (G-CSF) and antibiotics.

In July 2001, three months following her initial presentation, the patient developed fever, recurrent hypercalcemia 16 mg/dl and generalized maculopapular rash. A skin biopsy revealed infiltration of the dermis by atypical lymphocytes with the same profile (CD2, CD3, CD4). Sixty percent of the cells were also positive for Ki-67, a marker of high proliferative index. The patient did not respond to chemotherapy with cytarabine, cyclophosphamide, high-dose methotrexate and fludarabine and died.

Case 2. A 56-year-old female was born in Bucharest, Romania and immigrated to Israel

16 years ago. She was hospitalized in July 2003 because of progressive weakness started two weeks ago, and hypercalcemia 15.1 mg/dL. She had no history of intravenous drug abuse or recent travel. The physical examination disclosed mild generalized lymphadenopathy and splenomegaly. Blood count showed Hb 12.5 g/dL, WBC $18.5 \times 10^9/L$ with 69% lymphocytes, PLT $720 \times 10^9/L$. Peripheral blood and bone marrow contained >70% medium-sized lymphocytes showing pleomorphic multilobulated nuclei, some of them with flower-shaped occurrence. The lymphoid markers were CD3 64%, CD4 90%, CD25 85%. The cytogenetic analysis showed complex alterations: 48,XX,+3,der(10),t(10;15)(q23;q22),+mar[11]. Antibodies to HTLV-1 were found by ELISA and confirmed by Western blot (INNO-LIA, Innogenetics, Belgium). The diagnosis of ATL was established. The patient was treated by the chemotherapy LSG15 regimen, suggested by Japan Clinical Oncology Group for treatment of acute ATL.⁴ Hematological and cytogenetic remission was achieved and lasted for 4 months. Then prompt relapse occurred, accompanied by refractory hypercalcemia, and the patient died. Her family serological testing revealed that mother, sister and brother (leaving in Romania) are carriers of HTLV-1.

Additional studies

Rearrangement of TCR gamma chains, tested by PCR method using primers for the corresponding gene (5'-GCT TCT AGC TTT CCT GTC TC-3') (Genset corp, Paris, France) and Jurkat cell control had detected monoclonality of T-cells (Figure 1). DNA extracted from periph-

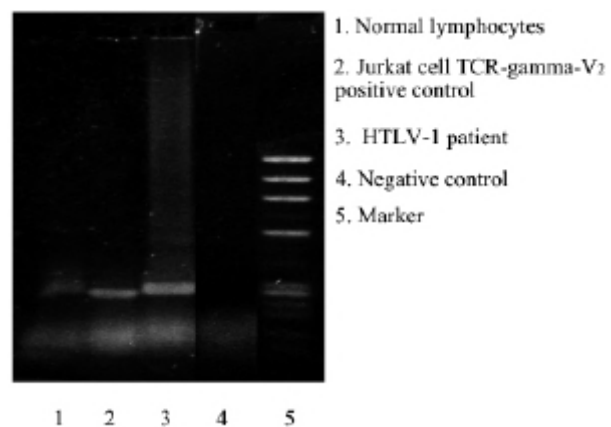


Figure 1. Detection of TCR gamma rearrangement by PCR rearrangement in HTLV-1 patient.

eral lymphocytes in case 1 was analyzed by quadruplicate inverse PCR as previously described⁵ (kindly performed by Dr. E. Wattel, Claude Bernard University, Lyon, France) and revealed sequences of the HTLV-1 genome (Figure 2).

Discussion

We report two patients of Romanian origin who developed acute type T-cell leukemia/lymphoma associated with the retrovirus HTLV-1. The transmission of the virus occurs by transfer of infected CD4+ lymphocytes from mother to child during breast-feeding, during sexual intercourse or by blood transfusion.³ The virus is endemic in Japan, West Africa and South America but is very rare in the US, Europe and the Middle East including Israel. In Israel, the antibodies to HTLV-1 were discovered in 5 out of 276.000 blood donations (0.0018%) [Israeli Central Blood Bank, 2002], however, 1.3% intravenous drug abusers were found seropositive.⁶ A very high rate of infection ~20% has been identified among a segregated community of Jews originated from the city of Mashhad in the northern Iran.⁷ ATL is extremely rare in Israel. The first Israeli patient was referred to the US in 1981 because of unexplained hypercalcemia. He developed diffuse lymphadenopathy, lymphomatous leptomeningitis and died.⁸ Another 49-year-old woman, who presented with smoldering disease involving skin only, turned to fulminant generalized leukemia and died from *Pneumocystis carinii* pneumonia.⁹ Four other cases were diagnosed in Mashhadi Jews, all of them demon-

strated a rapid and fatal disease course.¹⁰

In Romania, antibodies to the HTLV-1 were found in 0.64% of the blood donors indicated a 25-50-fold higher seroprevalence rate compared to other areas of Europe and the US.¹¹ Only occasional ATL cases were reported in Romania.¹²⁻¹⁴ So, our present report of 2 patients originated from Romania is important to assess the epidemiology of the disease. The finding of seropositivity of mothers in both patients supports the mother-to child transmission of the virus.

According to the clinical picture ATL has been classified into four types: smoldering, chronic, lymphomatous and acute.³ Our patients are typical of the acute type and manifested many of the clinical features of this disorder including the abrupt onset of fever, night sweats, hypercalcemia, osteolytic bone lesions, lymphadenopathy, splenomegaly and skin involvement. As determinative feature, acute type of ATL is characterized by the appearance of pleomorphic atypical lymphocytes on peripheral blood smear showing markedly lobulated nuclei (including so-called *flower cells*), which display membrane markers of mature peripheral T-cells: CD2, CD3, CD4, CD5 with the activated antigen CD25 and lack of CD7 and CD8. Patients with acute type ATL have very poor prognosis, only 17% survive 5 years, and the median survival is 10 months.⁴ Cause of death is often opportunistic infection. No treatment strategy has been found successful for the management of acute ATL. The LSG15 regimen, given to the second patient reported herein, has shown reasonable improvement in overall survival.⁴ Novel therapeutic strategies, more specific for T-line expansion, such as purine analogs or monoclonal antibodies, have been subject for clinical trials in ATL.⁴ The antiretroviral therapy with combination of interferon alpha and zidovudine had a beneficial effect even in patients refractory to chemotherapy.¹⁵ However, all of these regimens induced very few long-term survivors.

In conclusion, we describe two ATL patients originated from Romania and believe that this report has an important epidemiological significance.

Mordechai Shalrid,¹ Lev Shvidel,¹ Roman Korenfeld,¹ Adrian Duek,¹ Zvi Landau,² Alain Berrebi¹

¹Department of Hematology, ²Department of Internal Medicine D, Kaplan Medical Center, Rehovot, Israel, Affiliated to the Medical School of the Hebrew University, Jerusalem, Israel

*Correspondence: Prof. Alain Berrebi,

Department of Hematology, Kaplan Medical Center, Rehovot, 76100, Israel

Tel: +972-8-9441383 - Fax: +972-8-9441706

E-mail: alain_b@clalit.org.il

Keywords: HTLV-1, Adult T cell Leukemia/ Lymphoma, epidemiology

Figure 2. Quadruplicate inverse PCR performed in case 1 (sample PH1220). A unique dominant signal detected four times was obtained with the DNA. Such result demonstrated the monoclonal integration of the HTLV-1 provirus.

References

- Poiesz BJ, Ruscetti FW, Gazdar AF, Bunn PA, Minna JD, Gallo RC. Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T-cell lymphoma. *Proc Natl Acad Sci U S A* 1980; 77: 7415-9.
- Yoshida M, Miyoshi I, Hinuma Y. Isolation and characterization of retrovirus from cell lines of human adult T-cell leukemia and its implication in the disease. *Proc Natl Acad Sci USA* 1982; 79: 2031-5.
- Gessain A. Lymphoproliferations associated with human T-cell leukaemia/ lymphoma virus type I and type II. In: *Textbook of malignant haematology* (Dedos L, Linch D.C.,

- Lowenberg B, eds). London, Martin Duniz Ltd, 1999: 227-47.
4. Yamada Y, Tomonaga M. The current status of therapy for adult T-cell leukaemia-lymphoma in Japan. *Leuk Lymphoma* 2003; 44: 611-8.
5. Mortreux F, Leclercq I, Gabet A, Leroy A, Westhof A, Gessain A, Wain-Hobson S, Wattel E. Somatic mutation in human T-cell leukemia virus type1 provirus and flanking cellular sequences during clonal expansion in vitro. *J Natl Cancer Inst* 2001; 93: 367-77.
6. Maayan S, Dan M, Marlink R, Chen YM. HTLV among Israeli intravenous drug abusers. *Int J Epidemiol* 1992; 21: 995-997.
7. Miller M, Achiron A, Shaklai M, Stark P, Maayan S, Hannig H, Hunsmann G, Bodemer W, Shohat B. Ethnic cluster of HTLV-I infection in Israel among the Mashhadi Jewish population. *J Med Virol* 1998; 56: 269-74.
8. Blayney DW, Jaffe ES, Fisher RI, Schechter GP, Cossman J, Robert-Guroff M, Kalyanaraman VS, Blattner WA, Gallo RC. The human T-cell leukemia/lymphoma virus, lymphoma, lytic bone lesions, and hypercalcemia. *Ann Intern Med* 1983; 98: 144-51.
9. Leor J, Langevitz P, Trau H, Schinder EO, Douer D, Ben-Bassat I. HTLV-I-associated T-cell leukemia/lymphoma in Israel. *Isr J Med Sci* 1988; 24: 397-400.
10. Sidi Y, Meytes D, Shohat B, Fenig E, Weisbord Y, Lee H, Pinkhas J, Rosenblatt JD. Adult T-cell lymphoma in Israeli patients of Iranian origin. *Cancer* 1990; 65: 590-3.
11. Paun L, Ispas O, Del Mistro A, Chieco-Bianchi L. HTLV-I in Romania. *Eur J Haematol* 1994; 52: 117-8.
12. Veelken H, Kohler G, Schneider J, Dierbach H, Mertelsmann R, Schaefer HE, Lubbert M. HTLV-I-associated adult T cell leukemia/lymphoma in two patients from Bucharest, Romania. *Leukemia* 1996; 10: 1366-9.
13. Motoiu IR, Pecek MM, Dumitrescu A, Colita A, Necula A, Moldoveanu E, Colita D. Introduction to the study of adult T-cell leukemia and HTLV-I seropositivity in Romania. *Rom J Intern Med* 1993; 31: 199-205.
14. Lin BT, Musset M, Szekeley AM, Alexandre J, Fraitag S, Bodemer C, Charpentier A, Frenoy N, Misset JL, Medeiros LJ, Rappaport H. Human T-cell lymphotropic virus-1-positive T-cell leukemia/lymphoma in a child. Report of a case and review of the literature. *Arch Pathol Lab Med* 1997; 121: 1282-6.
15. Hermine O, Allard I, Levy V, Arnulf B, Gessain A, Bazarbachi A; French ATL therapy group. A prospective phase II clinical trial with the use of zidovudine and interferon-alpha in the acute and lymphoma forms of adult T-cell leukemia/lymphoma. *Hematol J* 2002; 3: 276-82.