Iranian Journal of Medical Sciences / Vol. 17, Nos. 3 & 4, December 1992

# CLINICAL MANIFESTATION OF ADULT-T-CELL LYMPHOMA/LEUKEMIA ASSOCIATED WITH HTLV-1 IN NORTH-EASTERN IRAN

R. Farid*, A. Shirdel*, Z. Tabei**

*Departments of Immunology and Hematology,*
**Mashhad University of Medical Sciences, Iran and*
***Shiraz University of Medical Sciences, Shiraz, Iran.*

**ABSTRACT** *The association of adult T cell lymphoma-leukemia and progressive myelopathy with human T lymphotropic virus type I (HTLV-1) has been proved. Several areas in the world are considered to be endemic areas for this virus. Our survey of the general population, as well as a study of 13 cases of lymphoma/leukemia in Khorasan province , may confirm this region or others in Iran as part of the endemic area.*

**Key words:** Lymphoma; leukemia; T cell; HTLV; myelopathy.

## *Introduction*

Human T lymphotropic virus type I (HTLV-1), discovered in 1980,[5] is considered to be the etiologic agent of adult T-cell lymphoma-leukemia (ATL).[8,9] This lymphoproliferative malignancy, occurring in the high endemic area for HTLV-1 (Japan, the Caribbean), is characterized by a clonal expansion of CD4 positive lymphocytes associated with a monoclonal integration HTLV-1 provirus in the tumoral cells.[12]

The retrovirus is transmitted mainly by blood transfusion and body fluids (sexual routes, breast feeding). The virus is also considered as an etiologic agent for spastic paralysis. Iran, especially Khorasan province located in the north-east of Iran, was considered as one of the endemic regions, when one of the authors diagnosed three cases of lymphoma-leukemia, which were associated with hypercalcemia and blast morphology, resembling adult T-cell lymphoma-leukemia. The high incidence of progressive myelopathy, as well as several cases of recently diagnosed lymphoma-leukemia associated with hypercalcemia, and a report of 4 cases of Jews from Mashhad, Iran, who emigrated to Israel, prompted us to develop a prospective study and survey of the general population as well as one on lymphoma-leukemia and myelopathy cases. The present communication is the first part of the report of this study.

**Table I.** Clinical characteristics of 13 patients

| Patient No. | Initial signs | Lymph-adenopathy | Hepato-splenomegaly | Hyper-calcemia | Skin lesion | Bone lesion |
|---|---|---|---|---|---|---|
| 1 | Hypercalcemia | + | + | + | - | - |
| 2 | Hypercalcemia | - | + | + | - | + |
| 3 | Skin lesion | + | + | + | - | - |
| 4 | Hypercalcemia | + | - | + | + | + |
| 5 | Hepatomegaly | + | + | + | - | - |
| 6 | Hypercalcemia | + | + | + | - | + |
| 7 | Skin lesion | + | + | + | + | - |
| 8 | Skin lesion | + | + | + | + | - |
| 9 | Skin lesion | + | + | + | + | - |
| 10 | Skin lesion | + | + | + | + | - |
| 11 | Hypercalcemia | + | + | + | - | - |
| 12 | Adenopathy | + | + | + | - | + |
| 13 | Hypercalcemia | - | - | + | - | - |

## *Materials and Methods*

We reviewed the records of 13 patients with T-cell lymphoma/leukemia and natural antibodies to human lymphotropic virus type 1 who were admitted to Ghaem Hospital Medical School, Mashhad, Iran during a 48 month period (1988-1991).

These cases were identified by different approaches including physical examination, peripheral blood count, lymph nodes and bone marrow biopsy.

HTLV-1 antibody assays in which three tests were used to detect HTLV-1 antibodies, namely:

(a) HTLV-1 antibodies on serum by passive particle-agglutination test (serodia-HTLV-1 Japan).
(b) ELISA (AKZO-Belgium).
(c) Western blot (Dupont, Wilmington, U.S.A.), which only confirmed positive sera.

An immunologic marker analysis of peripheral blood was performed with an E-rosette. T-cells ranged from 50 to 90 percent (Table II). In all 14 patients the neoplastic cells were observed in peripheral blood, bone marrow,and lymph nodes.[5]

## *Results*

The 13 patients were generally middle-aged, (median age 51, range 35 to 67 years). Of the 7 females and 6 males, 8 patients had been born in Mashhad and five in other cities of Khorasan province. None of the patients had a family history of malignant lymphoma or leukemia.

Table II. Hematologic and immunologic characteristics of 13 patients

| Patient No. | Antibody to HTLV-I | White cell count | E-rosette % of T-cells |
|---|---|---|---|
| 1 | + | 120.000 | 85 |
| 2 | + | Normal | 70 |
| 3 | + | 20.000 | 73 |
| 4 | + | Normal | -- |
| 5 | + | 12.000 | -- |
| 6 | + | 30.000 | 50 |
| 7 | + | 700.000 | 62 |
| 8 | + | 120.000 | 50 |
| 9 | + | 60.000 | 70 |
| 10 | + | 20.000 | -- |
| 11 | + | 10.000 | -- |
| 12 | + | 15.000 | 90 |
| 13 | + | 180.000 | 90 |

The symptoms generally began abruptly and the patients often had cutaneous lesions.

Two patients presented with large, discrete tumor and three with smaller (1 cm or less) nodules.

All patients had hypercalcemia. (Table I). The clinical manifestations of 13 patients are shown in Table I.

Circulating malignant cells were easily recognized in 10 patients at presentation, although 9 had elevated white cell counts (Table II).

An immunologic analysis of peripheral blood was performed with an E-rosetted T-cell count. HTLV-1 antibody assays were performed by ELISA (AZKO-Belgium) and passive particle. Agglutination test (Serodia-HTLV-1, Japan) and the positive sera were confirmed by western blot analysis (Fig. 1).

Hematological and immunological results are shown in Table II.

## *Discussion*

Adult T-cell lymphoma/leukemia is one of several clinical entities caused by HTLV-1 virus.[6,11] Manifestations include lymphadenopathy, hepatosplenomegaly, frequent skin involvement, lytic bone lesions, hypercalcemia, and high incidence of opportunistic infections.[1] The current series is the second report of ATL in residents of Mashhad, Khorasan province in north-eastern Iran.[7]

The true prevalence of HTLV-1 infection in Iran is still unknown.

All 13 patients had the clinical features of retrovirus-associated adult T-cell lymphoma/leukemia.

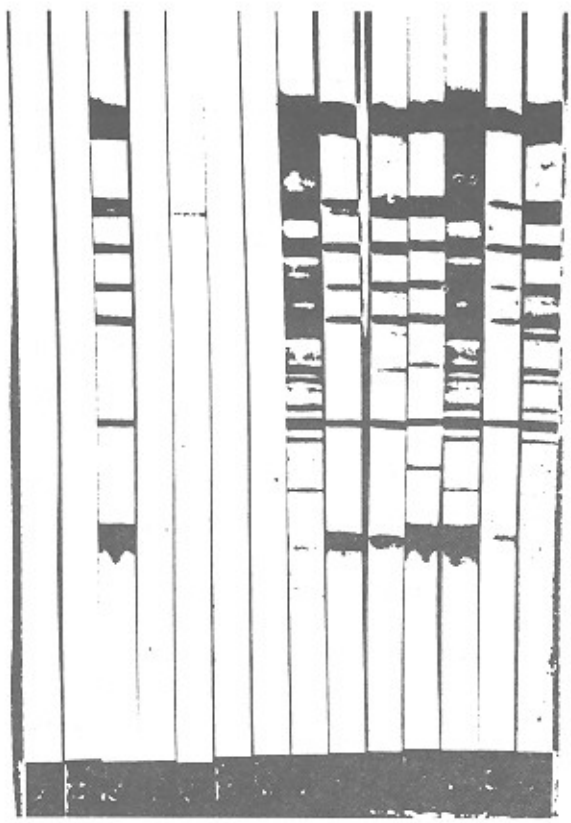

Figure 1. Western blot analysis from 3 ATL patients

The major clinical features of our study include hypercalcemia on an aggressive course characterized by the acute onset of symptoms by rapid dissemination and sometimes by infiltration of the skin (Tables I). Our patients were born in Khorasan Province which is an area where human T-cell lymphoma virus is known or suspected to be endemic (Farid, et al. unpublished data).

In our patients the onset of symptoms was acute, some rapidly developing skin lesion or hypercalcemia and increased bone turnover leading to metabolic and lytic bone lesions.

Hypercalcemia was present in all 13 cases. The frequency of hypercalcemia in our series was higher than that reported in Japan and similar to that in the Caribbean and United States cases.[1,2,4,10]

Peripheral lymphadenopathy and hepatosplenomegaly were common in our patients.

Biopsies of enlarged lymph nodes invariably confirmed the diagnosis of malignant lymphoma.

The main immunological and hematological characteristics are summarized in Table II.

In conclusion, retrovirus-associated T-cell lymphoma/leukemia seems to be more frequent in this part of Iran, because HTLV-1 may be endemic in the region.

Patients who present with the acute onset of generalized skin lesion or hypercalcemia with metabolic bone abnormalities should be strongly suspected of T-cell lymphoma/leukemia associated with HTLV-1.

The presence of HTLV-1 antibodies is an important factor in establishing the diagnosis.

## Acknowledgment

*The authors thank Dr.B.Safai for his excellent assistance and his laboratory staff at Cornell University, New York, for helping us to do western blot on our samples.*

## References

1. Blattner WA, Kalyanaraman VS, Roberrt-Guroff M, et al.: The human type C retrovirus, HTLV, in blacks from the Caribbean and relationship to adult T-cell leukemia/lymphoma. *Int J Cancer 1982;* **30**:257-64.
2. Catovsky D, Graves JF, Rose M, et al.: Adult T-cell lymphoma/leukemia in blacks from the West Indies. *Lancet 1982;* **1**:639-43.
3. Farid R, Etemadi M, Baradaran H, et al.: Screening sera from the adult population of Mashhad and Gonbad for antibodies to HTLV-I (submitted for publication).
4. Paul C, Bunn JR, et al.: Clinical course of retrovirus-associated adult T-cell lymphoma in the United States. *New Engl J Med 1983;* **309**:258-264.
5. Poiesz BJ, Ruscetti FW, Gazdar AF, et al.: Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T-cell lymphoma. *Proc Ntl Acad Sci USA 1980;* **77**:7415-7419.
6. Rosenblatt ID, Chen ISY, Wachsman W: Infection with HTLV-I and HTLV-II: Evolving concepts. *Semin Hematol 1988;* **25**:236-246.
7. Tabei SZ, Shirdel A: Adult T-cell leukemia/lymphoma in north-eastern Iran. *Iran J Med Sci 1986;* **13**:2-4.
8. Takatsuki K, Uchiyama T, Sagawa K, et al.: Adult T-cell leukemia in Japan. In: *Topics in Hematology*, Seno S, Takaku F, Irino S (eds): Excerpta Medica, Amsterdam: 1977; 73-77.
9. Takatsuki K: Adult T-cell leukemia (ATL): an overview. In: Roman GC, Vernant JC and Osame M, (eds), *HTLV-I and the nervous system. Neurology and Neurobiology*, New York, Alan R Liss Inc 1989; 51:57-63.
10. Uchiyama T, Hodoi J, Sagawa K, et al.: Adult T-cell leukemia: Clinical and hematologic features of 16 cases. *Blood 1977;* **50**:481-92.
11. Urta WJ, Lango DL: Clinical spectrum of human retroviral-induced disease. *Cancer Res 1985;* **45**:46375-46435.
12. Yamaguchi K, Seiki M, Yoshida M, et al.: The detection of human T-cell leukemia virus proviral DNA and its application for classification and diagnosis of T-cell malignancy. *Blood 1984;* **63**: 1235-1240.