

## Adult T Cell Leukemia / Lymphoma in Chile

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### RESUMEN

Se describen las características clínicas y de laboratorio de 26 pacientes chilenos caucásicos, con leucemia/lymphoma T del adulto, asociado a HTLV-1 (LLTA). El criterio diagnóstico incluyó características clínicas, morfología celular, inmunofenotipo, serología para HTLV-1 y/o análisis de ADN por Southern blot o PCR. De acuerdo a la presentación clínica, 12 casos presentaron la forma aguda de LLTA, 6 el tipo linfoma, 4 la forma crónica y 4 la forma latente. La edad media de presentación fue de 50 años, menor que los pacientes japoneses, pero significativamente mayor que los pacientes de otros países sudamericanos (ej. Brasil, Jamaica, Colombia). Las características clínicas más importantes como adenopatías, lesiones cutáneas y hepatoesplenomegalia, fueron similares en frecuencia a aquellas de otros países, excepto por la alta incidencia de enfermedad neurológica asociada. La paraparesia espástica se observó en un tercio de nuestros pacientes (8/26). El inmunofenotipo T se demostró en los 26 casos y la serología para HTLV1 fue positiva en 25/26. El análisis molecular del paciente seronegativo mostró integración monoclonal del ADN proviral en el ADN de los linfocitos y por lo tanto puede haber sido un mal respondedor a la infección retroviral. La integración del ADN proviral fue demostrada en 15/16 pacientes estudiados, siendo clonal en 10, policlonal en 3, todos ellos con enfermedad de tipo latente y oligoclonal en 1. En resumen, la LLTA en Chile tiene características clínicas y de laboratorio semejantes a las observadas en otras partes del mundo, excepto por una menor edad que los pacientes japoneses, pero mayor que la de los otros países latinoamericanos y una alta incidencia (31%) de pacientes con paraparesia asociada. El

análisis morfológico y de inmunofenotipo de los linfocitos anormales circulantes, junto con la documentación de la serología para HTLV- 1 y/o el análisis de ADN, son los exámenes claves para la identificación de esta enfermedad.

### Introduction

Adult T-cell leukemia/lymphoma was originally described in Japan (UCHIYAMA 1997) and the Caribbean region (BLATTNER 1982). Later on, several reports came from Latin American countries, specially from Brasil, Colombia, Peru, Argentina and from Afro-Caribbean immigrants to the United States and Europe (Pombo de Oliveira 1995, Blank 1996, Rodriguez 1994, Gioseffi 1995, Bunn 1983, Catovsky 1982, Gibbsw 1987, Manns 1993). In Chile, the first case of ATL of the acute form was documented in 1985, although without virological confirmation (Pereira 1985) and later on, it was published a case of a chilean man from Valparaiso that was living in Spain (Montserrat 1989). In the 90's, our group documented 4 cases with ATL and neurological signs (Cabrera 1991, Cartier 1995), and also 9 ATL cases (Cabrera 1994).

We refer our experience in Chile with 26 patients with ATL, from 1989 to 1998, describing the clinical and laboratory features, comparing them with those described in other parts of the world.

### Material and method

We have studied 26 patients born in Chile from 1989-1998, phenotypically caucasian, with HTLV1 positive ATL. The diagnosis was made based on clinical and laboratory features, HTLV- 1 serology and DNA analysis, documenting the presence of specific sequences of the virus on the neoplastic cells.

The immunophenotype was studied on mononuclear cells from peripheral, bone marrow or fluid cells obtained through ficoll-hypaque and stained with a panel of monoclonal antibodies. They were analysed in an immunofluorescence microscope Leitz Laborlux K or a flow cytometry.

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The detection of HTLV-1 was made by the determination of serum antibodies with ELISA (Biotech Research Laboratories) and particle agglutination (Serodia, Fujirebio, Japan) and also by detecting proviral DNA. This was made by Southern blot in mononuclear cells, using the probe pCH 1 for the gen env-pol of HTLV- 1 (donation of M. Reitz). The study of the virus in paraffin embeded tissue was done by polimerase chain reaction (PCR) analysis (probes donated by Prof. T. Schultz).

## Results

### *Clinical features*

The main clinical features are described in Table 1. Every patient was born in Chile. Most of them were from Santiago, 3 from far north (Antofagasta and Iquique), 2 from La Serena (north of Santiago) and 4 from Valparaíso (the port, west of Santiago). Four patients had been transfused previously 5, 17, 21 and 25 years, before the diagnosis of ATL was made and 9 had recurrent former infections, mainly pneumocistis carinii pneumonia. The median age was 50 years old (range 24-78) and there was equal number of men and women. The clinical forms of ATL were: acute 12 (46%), lymphoma 6 (23%), chronic 4(15.5%) and smouldering 4(15.5%). Two patients with the chronic form and 2 with lymphoma, evolved into an acute phase. Lymphadenopathy, hepatosplenomegaly and/or skin involvement was observed in more than half of the patients. The skin lesions presented as maculopapulas or nodules in 7 patients and generalized erythrodermia in other 5. Eight patients (31%) presented neurological symptoms, 7 of which were classical spastic paraparesis. The diagnosis of An and HAM/TSP was performed simultaneously in 3 cases, in 2 other the leukemia presented 1 and seven years before the paraparesia and in the other 2 the paraparesia preceded in 9 and three years the presentation of an acute and chronic leukemia respectively. This last patient had received a blood transfusion two years before the onset of the HAM/ TSP. Other clinical manifestations included: liver involvement (4 cases), small intestine (1 case), parotid (1 case), brain and meninges (1 case).

Morphology of peripheral blood lymphocytes was the key of diagnosis in the leukemic cases. Most of them were typical flowers cells and there was also some immunoblasts. The bone marrow was not infiltrated in 12/19 cases and there was only a slight

lymphocytic infiltrate in 7. The lymph node histology showed a lymphoid infiltration with a mixed diffuse pattern in 6 cases, pleomorphic in 3, large cells in 3, anaplastic cells like Hodgkin in 2 and small cleaved in 2. The skin biopsy showed dermic lymphoid infiltration with convoluted cells in 2 cases and in 4 other cases there was epidermotrophism and Pautrier microabsceses.

The treatment of these patients included: CHOP (Cliclofosphamide, Doxorubicine, Vincristine and Prednisone) 3-6 cycles in 9 cases, C-MOPP (Ciclofosphamide, Vincristine, Procarbazine, Prednisone) 8 cycles in 1 case, ProMace-Cytabom (Ciclofosphamide, Doxorubicine, Etoposide, Cytarabina, B leomicine, Vincristine, Metotrexate, Leucovorine, Prednisone) in 1 and Clorambucil in 2. Four patients with the acute form got no treatment. The response was short and transiet in 6 (less than four months). All the lymphoma patients responded, 2 had a complete remission and 4 a partial remission. Median survival in the acute cases was four months (<1-15 months) and all have died. The lymphoma cases, the median survival was 33 months, 2 are alive in complete remission five and six years after diagnosis. In the chronic cases, survival was 15 months and in the smouldering eight years. The most common cause of death for the acute and lymphoma cases was refractory hypercalcemia, renal failure or fulminat hepatic failure. The smouldering cases died due to respiratory infections.

### *Immunophenotype*

A T cell phenotype was demonstrated in all 26 cases studied, with expression of CD3 in 19/21 and CD2 in 2/3 of the cases (Table 2). The cells of 16/19 patients showed a CD4+/CD8- phenotype, in 2 both markers were negative and in the other both were positive. CD25 was positive in 8/14 cases and 7/19 expressed HLA-DR. B-cell markers (CD19 and surface Ig) were negative in every case. The immunoperoxidase study of the affected tissue in 4 cases (n° 8, 18, 19, 20), showed the expression of CD45 RO (UCHL1) in the lymphoid cells, while it was negative in the anaplastic Hodgkin-like cells in 2 of them (n° 18, 20). CD20 was negative in the 4 cases.

### *HTLV-1 study*

Antibodies to HTLV- 1 were detected in the serum of all patients by ELISA and PA except in one case.

Molecular analysis by Southern blot, demonstrated proviral HTLV- 1 DNA in the leukemic cells of all the cases that were studied, including the seronegative case. The proviral integration on the leukemic cells, was clonal in 9/13 cases, policlonal in 3 (2 of them with a smouldering leukemia) and oligoclonal in 1. The PCR technic with specific probes for HTLV- 1, was positive in different organs studied in 4 patients, like lymph node, liver, spleen and duodenum (cases 8,18,19,20).

The familiar serology survey showed positive family members in 9 out of 12 patients, including the husband in 5 patients (cases 3,9,11,20,21), the wife in 2 (cases 7,22) and 6 /10 children of ATL mothers and the mother in 2 patients (cases 11,13). The wives of 3 patients (cases 4,15,17) were serologically negative for HTLV-1. The husband of patient n°20 has a HTLV- 1 (+) spastic paraparesis.

## Discussion

This study confirms that ATL is one of the lymphoproliferative diseases seen in Chile. The clinical and laboratory features of our patients with ATL are similar to those described in Japan, Caribe and other Southamerican countries, with the

exception of the median age of presentation. This was intermediate between that observed in Japanese and that in Caribbean patients or inmigrants from Caribe to England and that of other Southamerican countries. While in our group of patients the median age was 50 years old, in Japan is 59 (Uchiyama 1997) and in other Southamerican countries is 38-43 (Pombo de Oliveira 1995, Catovsky 1982). It was also noticeable the high association of ATL and TSP, the highest documented in the literature: 31%. We don't know whether this is associated with genetic and/or environmental factors.

In relation to the transmission of HTLV-1, our study demonstrates the three ways described: sexual from husband to wife and viceversa, from mother to child (cases 11 and 13) and through blood transfusion in a surgery five years before the development of a chronic ATL (case 15). This last patient was suffering from a ISP in the previous two years.

In summary, this study confirms the previous literature, that ATL is a rather prevalent disease in Chile, that there are similarities but also some differences with this entity described in other endemic regions, being the main one, the high frequency of An patients with associated HAM/ TSP in Chilean patients.

## REFERENCES

- BLATTNER, W.A., KALYANARAMA, V.S., ROBERT-GUROFF, M., LISTER, T.A., GALTON, D.A.G., SARIN, P.S., et al. The human type-C retrovirus, HTLV, in blacks from the Caribbean region and relationship to adult T-cell leukemia/lymphoma. **Int. J. Cancer.** 30: 257-64.
- BLANK, A. **Adult T-cell leukemia/lymphoma in Southwest Colombia.HTLV,Truths and Questions.** Edit Zaninovic.266-71.
- BUNN, SCHECHTER, G.P., JAFFE, E., BLAYNEY, D., 1983 YOUNG, R.C., MATHEWS, M.J., et al. Clinical courses of retrovirus-associated adult T-cell lymphoma in the United States. **N. Engl. J. Med.** 309: 257-64.
- CARTIER, L., CASTILLO, J.L., CABRERA, M.E., ARAYA, F., MATUTES, E., FORD, A.M., GREAVES, M.F. HTLV-1 positive progressive spastic paraparesis (TSP) associated with a lymphoid disorder in three chilean patients. **Leukemia and Lymphoma** 17: 459-64.
- CABRERA, M.E., GRAY, A.M., CARTIER, L., ARAYA, F., HIRSH, T.,FORD, A.M.; GREAVES,M.F. Simultaneous adult T-cell leukemia/lymphoma and sub-acute polyneuropathy in a patient from Chile. **Leukemia** 5: 350-53.
- CABRERA, M.E., LABRA, S., CATOVSKY, D., FORD, AM., 1994 COLMAN, S.M., GREAVES, M.F, MATUTES, E. HTLV-1 positive adult T-cell leukaemia/lymphoma (ATLL) in Chile. **Leukemia** 8: 1763-67.
- CATOVSKY, D., GREAVES, M.F., ROSE, M., GALTON, 1982 D.A.G., GOOLDEN, A.W.G., MCCLUSKEY, D.R., et al. Adult T-cell lymphoma leukaemia in blacks from West Indies. **Lancet** i: 639-43.
- GIBBS W.N., LOFTERS, W.S., CAMPBELL, M., HANCHARD, 1987 B., LAGRENADE, L., CRANSTON, B., et al. Non-Hodgkin lymphoma in Jamaica and its relation to Adult T-cell leukemia-Lymphoma. **Ann. Intern. Med.** 106: 361-684.
- GIOSEFFI, O.N., NUCIFORA, E., FANTL, D., DUFOUR, C. 1995 MILONE, J., DI PAOLO, H. D. Leucemia-linfoma T del adulto HTLV- 1 positiva en Argentina. **Sangre** 40: 421-24.
- MANNIS, A., CLEGHORN, F.R., FALK, R.T.,HANCHARD, 1993 B., JAFFE, E. S., BARTHOLOMEW, C., et al. Role of HTLV-1 in development of non-Hodgkin lymphoma in Jamaica and

- Trinidad and Tobago. **Lancet** 342:1447-50.
- MONTSERRAT, E., LOZANO, M., URBANO-ISPIZUA, A.,  
1989 MATUTES, E., FELIU, E., ERCILLA,  
G., et al. Adult T-cell Leukemia in a  
Chilean resident in Spain: long-lasting  
remission after 2-deoxycoformycin  
treatment. **Leuk. Lymphoma** 1: 47-49.
- PEREIRA, J., LIRA, P., GREBE, G., ROA, I. Leucemia/linfoma  
1985 del adulto. **Rev. Med. Chile** 113: 41-44.
- POMBO DE OLIVEIRA, M.S., MATUTES, E., SCHULTZ, T.,  
1995 CARVALHO, S.M., NORONHA, H.,  
REAVES, J.D., et al. T-cell malignan-  
cies in Brasil. Clinico-pathological and  
molecular studies of HTLV-I positive and  
negative cases. **Int. J. Cancer** 60(6): 823-  
7.
- RODRIGUEZ, W., MISAD, O., GARCIA, J. CASTRO DE LA  
1994 MATTA, VALLEJOS, C., CASANO-  
VA, L., et al. Síndrome leucemia/linfo-  
ma T del adulto (ATL) en el Perú. **Acta  
Cancerológica** 3: 7-20.
- UCHIYAMA, T., YODOI, J., SAGAWA, K., TAKATSUKI, K.,  
1977 UCHINO ,H. Adult T-cell leukemia:  
clinical and hematologic features of 16  
cases. **Blood** 50: 481-92.
- YAMAGUCHI, K. Human T-lymphotropic virus type in  
1994 Japan. Review article. **Lancet** 343: 213-  
16.