Acta Haematologica Polonica 49(2) • June 2018 • 75-84 • DOI: 10.2478/ahp-2018-0014

ORIGINAL RESEARCH ARTICLE/PRACA ORYGINALNA journal homepage: https://content.sciendo.com/ahp

Clinical and laboratory features of adult T-cell leukemia/lymphoma (ATL): a study of 37 cases

Article history:
Received: 18.09.2016
Accepted: 07.05.2018

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Abstract

Adult T-cell leukemia/lymphoma (ATL) related to the human T-cell lymphotropic virus type I (HTLV-I) is a malignant lymphoproliferative disease. ATL is classified in four subtypes: lymphoma, acute, smoldering and chronic. We analyzed, retrospectively, 46 consecutive patients with T-cell disease with ATL diagnosed from 1995 to 2007. ATL diagnose was confirmed in 37 of these patients. There were 26 females and 11 males (70% vs 30%, respectively, p = 0.014). The median age was 42 years old. Twenty-five were nonwhite and twelve were white (67.6% vs 32.4%, respectively, p = 0.033).Twenty two patients had the acute form, eight had chronic form and seven had lymphomatous form. Two of them had osteolytic lesions. There were two cases with pulmonary infiltrates; one patient had ATL associated to Hansen's disease. All cases had antibodies to HTLV-I confirmed by Western Blot, polymerase chain reaction (PCR) was performed in 22 cases. Flow cytometry revealed positivity for CD4 and CD25 in most cases. The mean and median overall survival time was 11.3 months and 2 months, respectively. The family´s study showed that 60% of the mothers were HTLV-I seropositive. These data emphasize the importance of a serologic screening for HTLV and immunophenotyping to differentiate ATL from others T-lymphoproliferative disorders.

Keywords:
HTLV-I, ATL, clinical characteristics, Brazil

Introduction

The human T-cell lymphotropic virus type I (HTLV-I) was discovered in 1980. It is the first oncogenic human retrovirus [29]. Several diseases have been found to be related to HTLV-I infection, as HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP), adult T-cell leukemia/lymphoma (ATL), polymyositis, uveitis and other inflammatory conditions [11, 23, 27, 35, 44].

The most common reasons for HTLV-I transmission are firstly the sexual activity, particularly from males to females, through blood transfusion of infected cells, and from breast feeding mother to child [8, 17, 20, 24, 37]. It is endemic in the Caribbean Islands, southwestern Japan, Papua New Guinea, Central Africa and South America, including Brazil.

Groups of peoples from various populations were studied in Brazil which showed prevalence of different types of HTLV antibodies [4, 31]. In several areas HTLV-I prevalence in blood donors ranges from 0.4 to 1.8% [9].

The first cases of ATL were reported in Kyoto in 1977, commonly occurring in patients from southwestern Japan [41, 44]. The major case series explaining the clinical spectrum of ATL comes from Japan [38, 46]. Most probably it takes many decades to show, with occurrence in 3-5% of infected individuals.

So far, the development of ATL has been mainly linked with early HTLV-I infectivity in life, most likely transmission from mother to child [43]. ATL presents four distinct clinical subtypes, according to clinical features: acute, lymphoma, chronic and smoldering [39]. The clinical and laboratory features of ATL include hepatomegaly, enlargement of the lymph nodes, splenomegaly, hypercalcaemia and frequent skin lesions; morphological appearance in peripheral-blood called "flower" cells (convoluted nucleus with polymorphism and multilobulation and scanty basophilic cytoplasm) and the presence of HTLV-I antibody. The characteristic surface phenotypes of ATL cells are CD4+, CD3+, CD25+ and CD8- [32].

The disease has a bad diagnosis owing to an intrinsic resistance of leukemic cells to standard or even high doses of chemotherapy in addition to a related severe immunosuppressant [2].

The data about the incidence and pathogenesis of ATL in Brazil showed the rate of HTLV-I positivity of 28.4% among the patients with T-cell disease [4] and ATL has been reported in many parts of the country [4, 32].

The objective of the study at hand is to investigate the laboratory and clinical features of the patients suffering from T-cell disease HTLV-I, suspected of ATL, carried out at HEMORIO, a reference center for hematologic diseases in Rio de Janeiro state.

Methods and material

Patients

Starting from January 1995 till December 2007, 46 patients with T-cell disease and HTLV-I positive, from HEMORIO electronic registry system, were selected and studied retrospectively. Special care was taken to record information of epidemiological features, sexual lifestyle, co-infection with other virus, and previous blood transfusion. The families of the HTLV+ patients were recruited under consent and 67 family members were investigated. The criteria for ethnic groups considered whites the Brazilians of European descent, and nonwhites all blacks and mulattoes, as well as mixed races of whites, Amerindian or blacks.

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The finding of ATL was established on clinical features, hypercalcemia, hematological findings, increased LDH value, detection of HTLV-I antibodies and immunophenotyping analyses. Four subtypes were used to classify the patients according to the classical criteria established by Shimoyama et al [39].

Morphology and immunophenotyping

Bone-marrow aspirate and/or peripheral-blood were examined in all cases according to Catovsky et al (1984). Immunophenotyping analyses were performed routinely using a clean peripheral blood mononuclear cell (PBMC) from the patients, by flow cytometry using a panel of fluorochrome-conjugated monoclonal antibodies including, CD2, CD3, CD4, CD7, CD8, CD25, CD30, CD38, HLADr, CD19 and CD45RO, for a four-color fluorescent analysis on a FACS facscalibur flow cytometer (BD Biosciences). For patients having leukemic signs, the criteria of T-cell type was accepted when above 25% of the circulating malignant cells were positive for T-cell markers [5, 32].

HTLV-I serological assays

Collected from the patients, the peripheral blood samples were checked for the occurrence of antibodies to HTLV-I and II by the help of the enzyme immunoassay (ELISA – Vironostika HTLV-I/II Organon Teknika, Boxtel, Holland), in accordance with the manufacturer's directions. Repeatedly reactive on ELISA specimens were further given to a Western Blot assay (HTLV BLOT 2.4 Genelabs Diagnostics Pte. Ltd., Singapore) for verification and type differentiation in accordance with manufacturer's guidelines. This examination classifies as HTLV-positivity with the sample reactive to, no less than, two distinctive HTLV structural gene products: *env* gD21 and/or gp46 and *gag* p24 and/or p19; viral type was described as HTLV-I or HTLV- II when reactive to recombinant gp46-I or gp46-II, respectively; as HTLV-indeterminate in case of the pattern not meeting the positivity criteria, and as negative in case of total reactivity absence.

HTLV-I molecular assays

Using the ficoll-hypaque density gradient centrifugation, peripheral blood mononuclear cells (PBMC) were separated, and extraction of DNA was done from PBMC using the QIAamp DNA Blood Mini Kit – Qiagen (Hilden Germany), in accordance with manufacturer's guidelines. Finding of HTLV-I sequences was carried out by PCR making use of specific primers for three distinguished HTLV genomic regions (*LTR*, *tax, pol*) as explained elsewhere [7, 36].

Statistical analysis

The 2 test was used to compare race and gender proportion in the analyzed group with a *p*-value of 0.05. Survival rates for each patient were calculated from diagnosis confirmation until death or censure. Data were analyzed with the use of the Kaplan-Meier Curve, and Comparisons among ATL subgroups were carried out using log-rank test (significance p-value 0.05). Every statistical test was done using the Statistical Package for the Social Sciences (SPSS) v.13.0 software (SPSS Inc, Chicago, II, USA).

Results

Clinical features

Forty-six patients with T-cell disease HTLV-I positive were diagnosed between January 1995 and December 2007. ATL was confirmed in 37 patients enrolled in this study. Among the ATL cases, 22 (59%) presented acute subtype, eight (22%) chronic subtype, seven (19%) lymphoma type and no cases of smoldering subtype were found. During evolution, nineteen of the patients with chronic or lymphoma type changed to acute subtype (Tab. I and II).

The main characteristics of the 37 ATL patients are summed up in table I, and II. The span of time between the showing of the symptoms and the diagnosis varied from eight days to five years (just the case 15). Generalized lymphoadenopathy, hepatomegaly, splenomegaly, skin lesions and hypercalcaemia were features present in many patients (Tab. II). Two of them had osteolytic lesions. There were two cases of pulmonary infiltrate (Fig. 1, case 15) and ten cases (27%) had central-nervous system involvement. One patient had ATL concomitant with Hansen's disease (Fig. 2, case one). Case eight illustrates the typical ATL skin lesion (Fig. 3).

Although HAM/TSP and ATL are distinguished clinical entities caused due to HTLV-I, there was one case of ATL concomitantly with HAM/TSP. This patient suffered from sphincter dysfunction, gate difficulty, and spastic paraparesis of the lower limbs, brisk reflexes and hyper-reflexia with HTLV-I antibodies found in the CSF. Each and every of these clinical symptom fulfilled the diagnostic criteria of HAM/TSP [18]. These signs began one year before ATL symptoms.

Laboratory features

The results of laboratory findings and risk factors were described in table I and II. Eighteen cases (49%) had an increased LDH levels; hypercalcaemia was present in 20 patients (54%). The range of white-blood-cell (WBC) counts goes from 2,090 to 425,000 k/µl. Cell morphology seems to be of nucleus shape and pleomorphic in size. Flower cells were found in twenty-three patients (62%) peripheral blood. In most cases, the Immunophenotyping by flow cytometry was positive for CD2, CD3, CD4, CD5, CD25, HLADr and CD45 and negative for CD7, CD8 and CD19, a typical T-cell phenotype. Co-expression of positive CD4 and CD8 was found in one case and in three patients the CD4 and CD8 were negative. In particular CD25 was negative in four cases**.** All cases had antibodies to HTLV-I confirmed by Western Blot; PCR was performed in 22 cases and the HTLV-I viral segment was detected in all of them.

Most of the patients (33 out of 37) received CHOP treatment (cyclophocphamide, doxorubicin, vincristine and prednisone). Only one patient who presented chronic form and two patients who presented acute form received CHOP, AZT and Interferon.

Survival analysis

Survival data were compared between the subtypes of ATL using the log-rank test and Kaplan-Meier to evaluate statistical significance. The period starting from the date of diagnosis till the moment of death or censure was defined as the survival time. Cases with

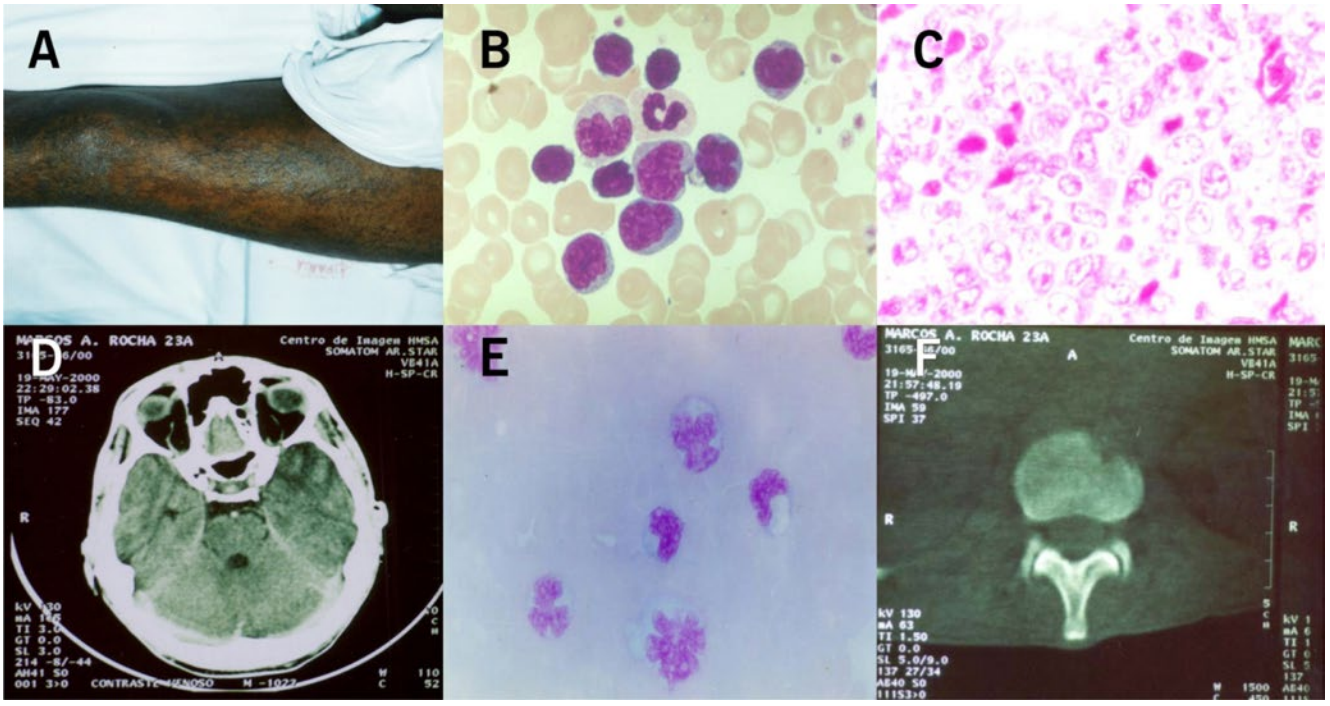

Fig. 1. Case 1: A. Skin lesion in patient with ATL associate to Hansen's disease. B. Flower cell in peripheral blood. C. Infiltrate by lymphocytes in lympho nodes. D. Central-nervous system involvement (blastic cells infiltration). E. CNS infiltration in cerebrospinal fluid. F. CT of lumbar with osteolitic lesions in the spine

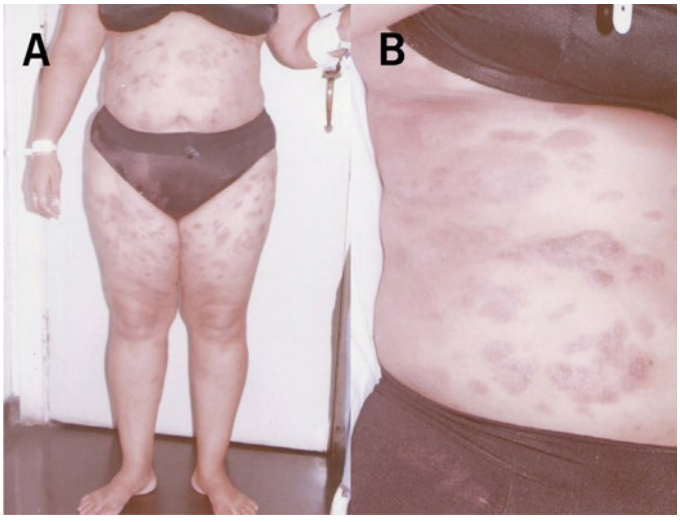

Fig. 2. Case 10: A and B. Skin infiltration in ATL patient

missing follow-up or which completed the follow-up period were censored alive at that time. Although one of the cases had exceeded the following five years (almost 7 years), the data were censored on the 60th month of observation.

Analyzing the curves, overall survival data were relatively short (median 2.0 months, 95% between 0 and 5.6 months). However, those with chronic disease had longer survival (median 15.0 months, 95% between 0 and 37.6 months). The lymphoma subtype group had the worst prognosis (median survival 1.0 month). Given the small number of cases, it was not possible to detect a statistically significant difference between groups (log-rank test 0.74). The major reason for death was advancement of the disease linked with hypercalcemia and infective complications (Fig. 4). Table describes clinical evolution.

Epidemiology

The age of ATL patient was found between 23 to 91 years, with an average of 42 years. There were 11 males (30%) and 26 females (70%), with significant differences regarding gender in the total group analyzed (p = 0.014). Twenty five (67.6%) patients were non-white

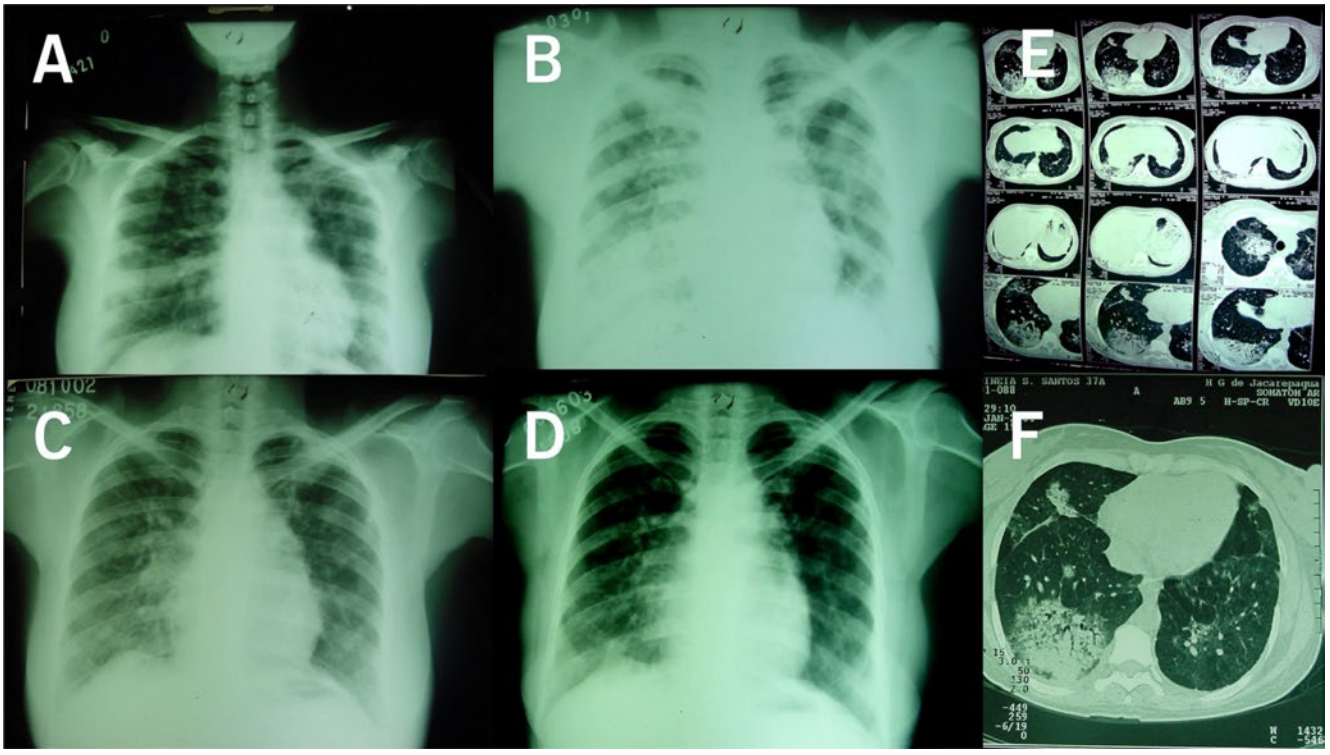

Fig. 3. Case 15: Pulmonary infiltration in ATL. Thorax X-ray in patient with ATL in different occasions. A. In 2000 and B in 2001 (before treatment). C. In 2002 (during the treatment). D. In 2003 (after treatment). E and F. CT of chest in 2001 at the diagnosis, showing pulmonary infiltration

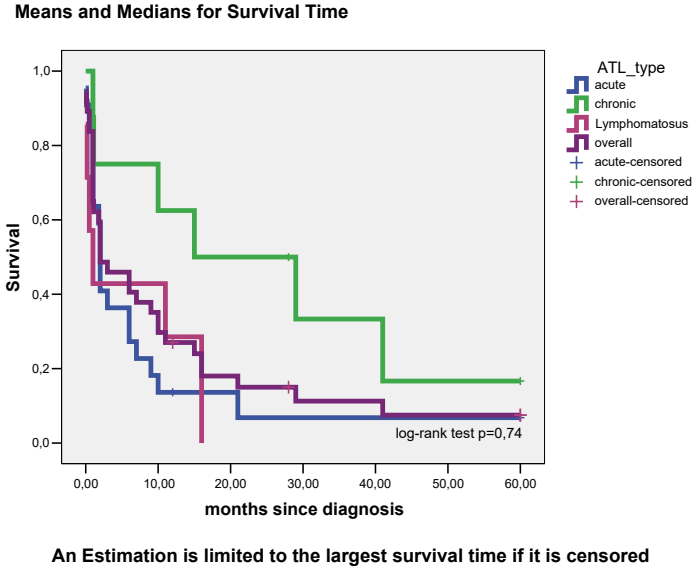

Fig. 4. Overall and specific ATL-subtypes survival analysis using KM curves and log-rank test

Table I. Demographic, ATL subtypes and epidemiological data

CASES		Ethnicity	HTLV- I		Risk factors		
			WB	PCR	HTLV I + Mothers	Breast-feeding (time/months)	Other risk factors/ epidemiological data
1.	23ys;M;ATL-a	NW	(+)	(+)	(+)	6 months	None
2.	24ys;M;ATL-1	NW	(+)	(+)	(-)	6 months + wetnurse	BD HTLV-I +
3.	25ys;F;ATL-1	W	(+)	Nd	Unknown	Unknown	Unknown
4.	26ys;M;ATL-1	NW	(+)	Nd	(+)	3 months	Sexual promiscuity; addicted
5.	26ys;M;ATL-a	W	(+)	(+)	(+)	Unknown	Unknown
6.	28ys;F;ATL-a	W	(+)	(+)	Unknown	Unknown	Addicted
7.	31ys;F;ATL-a	NW	(+)	(+)	(-)	12 months + wetnurse	HPV, HBV, sexual promiscuity
8.	34ys;F;ATL-a	NW	(+)	(+)	(+)	24 months	Addicted
9.	34ys;F;ATL-ca	W	(+)	Nd	(+)	3 months	None
10.	34ys;F;ATL-a	W	(+)	(+)	(+)	Unknown	BD HTLV-I +, HPV
11.	36ys;M;ATL-1	W	(+)	(+)	(+)	12 months	BD HTLV-I +
12.	36ys;F;ATL-a	W	(+)	Nd	unknown	Unknown	Unknown
13.	37ys;F;ATL-a	NW	(+)	(+)	(+)	Unknown	Unknown
14.	39ys;M;ATL-a	NW	(+)	Nd	Unknown	Unknown	Sexual promiscuity; HIV
15.	39ys;F;ATL-ca	NW	(+)	Nd	(Deceased)	Unknown	Anti-Hbc, herpes zoster
16.	39ys;F;ATL-a	NW	(+)	(+)	(+)	Unknown	None
17.	40ys;F;ATL-a	NW	(+)	(+)	(-)	24 months + wetnurse	None
18.	41ys;F;ATL-a	NW	(+)	(+)	(-)	30 months, wetnurse	None
19.	42ys;F;ATL-a	NW	(+)	Nd	(+)	Unknown	Mother with HAM/TSP
20.	43ys;F;ATL-a	NW	(+)	Nd	(Deceased)	24 months	None
21.	43ys;F;ATL-a	W	(+)	Nd	Unknown	Unknown	None
22.	44ys;F;ATL-a	NW	(+)	Nd	Unknown	Unknown	None
23.	45ys;F;ATL-a	NW	(+)	Nd	(+)	7 months	None
24.	46ys;M;ATL-ca	NW	(+)	Nd	Unknown	Unknown	Mother with myelopathy
25.	46ys;M;ATL-ca	NW	(+)	(+)	(+)	Unknown	Unknown
26.	47ys;F;ATL-1-a	NW	(+)	Nd	Unknown	Unknown	Blood transfusion + HCV
27.	48ys;F;ATL-a	NW	(+)	Nd	(+)	7 months	BD HTLV-I +
28.	48ys;F;ATL-ca	NW	(+)	(+)	Unknown	Unknown	BD HTLV-I +
29.	49ys;F;ATL-1-a*	NW	(+)	(+)	Unknown	Unknown	Blood transfusion
30.	57ys;F;ATL-a	W	(+)	(+)	Unknown	Unknown	Blood transfusion
31.	57ys;M;ATL-1-a	NW	(+)	(+)	Unknown	Unknown	None
32.	58ys;M;ATL-a	W	(+)	(+)	Unknown	Unknown	none (transferred to)
33.	60ys;F;ATL-a	NW	(+)	(+)	Unknown	Unknown	HCV
34.	70 ys;F;ATL-a	W	(+)	(+)	Unknown	Unknown	Unknown
35.	72ys;M;ATL-c	W	(+)	nd	(Deceased)	Unknown	Blood transfusion
36.	83ys;F;ATL-c	NW	(+)	(+)	(Deceased)	Unknown	Anti-HBc
37.	91ys;F;ATL-ca	NW	(+)	(+)	Unknown	Unknown	None

ATL-a – adult T-cell leukemia/lymphoma acute; ATL-c – adult T-cell leukemia/lymphoma chronic ; ATL-l – adult T-cell leukemia/lymphoma lymphoma
ATL-ca – adult T-cell leukemia/lymphoma chronic evoluted to acute-subtype; ATL-la – adult T-cell leukemia/lymphoma lymphoma evoluted to acute-subtype;
nd = not done; M – Male; F – Female; W – white; NW – non white; BD HTLV-I + – blood donor HTLV-I +; HAM/TSP – HTLV-I-associated myelopathy/tropical spastic paraparesis;
HIV – human immunodeficiency virus; HPV – human papilloma virus; HBV – hepatitis B virus; HCV – hepatitis C virus; * – not smoldering cases were found.

Table II. Clinical and laboratory features of ATL patients

Clinical Feature	ATL subtypes			Total
	Acute (n = 22)	Chronic (n = 8)	Lymphoma (n = 7)	37 (100%)
Lymphadenopathy	11	3	6	20 (54%)
Skin lesions	11	4	2	17 (46%)
Splenomegaly	8	1	1	10 (27%)
Hepatomegaly	13	1	0	14 (38%)
CNS infiltration	7	2	1	10 (27%)
Pulmonary infiltrate	0	2	0	2 (5%)
Osteolytic lesions	2	0	0	2 (5%)
Hypercalcaemia (> 10,3 mg/dl)	15	2	3	20 (54%)
LDH (> 480 u/l)	13	2	3	18 (49%)
WBC > 10 x 10/ml (> 10,2 k/µl)	23	5	3	31 (84%)
Atypical lymphocytes (flower cells)	19	2	2	23 (62%)
CD4 + (> 50%)	15	4	3	22 (59%)
CD25 + (> 15%)	12	4	2	18 (49%)

compared to twelve (32.4%) white. There were significant differences regarding ethnicity in the total group analyzed (p = 0.033).

According to the regional origin, the patients were from five different states of Brazil: thirty were from Rio de Janeiro, four from Bahia, one from Pernambuco, one from Maranhão and one from Pará.

Among the entire group, three of the patients were blood donor candidates that had positive HTLV-I antibody and were deferred from the blood banks. Three of them were drug users (cocaine), three others reported sexual promiscuity, and two patients had sexual transmissible diseases (STD) being identified as HPV. One of them developed uterus carcinoma during the ATL treatment. Four patients had been transfused before the ATL diagnosis, twelve patients were breast-fed by their mothers, and four patients were breast-fed by wet nurses and their mothers were HTLV-I negative. The time of breast-feeding varied from three months to two years (Tab. I).

Considering the study of 67 family members of the ATL patients: 19 mothers, seven spouses, 21 offspring, 20 siblings were analyzed for anti-HTLV antibodies. HTLV-I seropositivity was evident in 60% of the mothers, 40% of the spouses, 24% of the offspring and 24% of the siblings.

Discussion

ATL is a destructive T-cell malignance the primary cause of which is HTLV-I infection and it is commonly found in individuals from virus endemic regions, for example Brazil. In this country the disease represents approximately 28% of the cases of T-cell malignancies [4, 31].

The current study found that among the 46 patients with T-cell disease suspected of ATL, only 37 were confirmed as ATL. Although some studies in Japan and Jamaica have provided important data on pathologic and epidemiological characteristics of ATL, in Brazil there are some difficulties in the diagnosis of this disease, due to the similarities with other T-lymphoproliferative disorders [16, 32, 45]. The clinical features of ATL in Brazil are similar to cases from the Caribbean and Japan [16, 32, 46] and among our series of ATL patients we found the similar clinical manifestation as reported in others Brazilian studies [3, 32]. Co-expression of positive CD4 and CD8 was found in one case and in three patients the CD4 and CD8 were negative. In particular CD25 was negative in four cases. These rare immunophenotypic variants were previously reported [32]. Hypercalcaemia was present in 54% of the cases, two patients presented osteolytic lesions and 37% of the patients presented CNS involvement. One patient, besides neurological disease had disseminated osteolytic lesions and Hansen's disease, as previously reported [14, 15, 25].

In accordance with the disease presentation form, our results are similar to the data reported by Schimoyoma [39] where the frequency of ATL subtypes presents acute form 57%, lymphomatosis 19%, chronic 19% and smoldering 5%, except in smoldering form, where no case was found.

Most of the patients (33 out of 37) received CHOP treatment (cyclophocphamide, doxorubicin, vincristine and prednisone). Only one patient who presented chronic form and two patients who presented acute form received CHOP, AZT and interferon. The protocol for ATL in the institution is CHOP, but at the time of the research ATL treatment was not available for all patients, which was released on July 19th, 2016, according to protocol 58998 of Brazilian Health Ministry.

ATL has a bad outcome because of an intrinsic resistance to leukemia cells to standard or even elevated doses of chemotherapy, furthermore also to a linked severe immunosuppressant. Hence, the probable function of typical chemotherapy, a greater dose of chemotherapy, with allogenic or autologous bone marrow transplantation is yet to be defined. Significant progress was observed with the combination of zidovudine (AZT) and interferon-alpha (IFN). As the cure is still not very clear, modern therapeutic tactics or new combinations are necessary to be

Table III. Clinical evolution of ATL patients

CASES/Diagnostic		Date	CHOP Treatment	Responded the treatment	Death causes	Opportunistic infections	Patients undergoing authopsis
1.	23ys;M;ATL-a	5/4/2000	Sim	50 days	Organic encephalopathy due to neoplastic infiltration + Hypercalcemia metabolic coma + pulmonary infection	Sim	No
2.	24ys;M;ATL-1	1/30/2002	Sim	16 months	Septic Shock	Sim	No
3.	25ys;F;ATL-1	4/17/2001	Sim	18 days	Septic Shock	Sim	No
4.	26ys;M;ATL-1		Sim			Sim	No
5.	26ys;M;ATL-a	10/29/2007	Sim	6 months	Organic encephalopathy due to neoplastic infiltration + pulmonary infection		No
6.	28ys;F;ATL-a	12/4/2006	Sim+AZT+Inter- feron	12 months	Alive		
7.	31ys;F;ATL-a	6/19/2002	Sim	7 months	Septic Shock + accute renal infection	Sim	No
8.	34ys;F;ATL-a	4/14/2000	Sim	1 months	Septic Shock	Sim	No
9.	34ys;F;ATL-ca	12/21/2001	Sim	41 months	Septic Shock	Sim	No
10.	34ys;F;ATL-a	10/13/2005	Sim	1 months	Septic Shock + accute renal infection	Sim	No
11.	36ys;M;ATL-1	5/29/1995		1 months (transferred to)			
12.	36ys;F;ATL-a	1/27/2005	Sim	17 months	Septic Shock + accute renal infection	Sim	No
13.	37ys;F;ATL-a	5/26/2007	Sim	6 months	Septic Shock	Sim	No
14.	39ys;M;ATL-a	11/18/1999	Sim	10 days	Septic Shock + neoplastic pleural effusion	Sim	No
15.	39ys;F;ATL-ca	8/28/2001	Sim	29 months	Septic Shock	Sim	No
16.	39ys;F;ATL-a	12/20/1996	Sim	21 months	Organic encephalopathy due to neoplastic infiltration + pulmonary infection	Sim	No
17.	40ys;F;ATL-a	5/18/2001	Não	7 days	Organic encephalopathy due to neoplastic infiltration + Hypercalcemia metabolic coma + Septic Shock	Sim	No
18.	41ys;F;ATL-a	5/15/2005	Sim	1 months	Septic Shock	Sim	No
19.	42ys;F;ATL-a	9/1/2006	Sim+AZT+Inter- feron	27 days	Septic Shock	Sim	No
20.	43ys;F;ATL-a	3/22/2001	Sim	81 months	Alive		
21.	43ys;F;ATL-a	2/10/2005	Sim	2 months	Septic Shock	Sim	No
22.	44ys;F;ATL-a	3/24/2002	Não	1 day	Organic encephalopathy due to neoplastic infiltration + Septic Shock	Sim	No
23.	45ys;F;ATL-a	8/1/2000	Sim	3 months	Septic Shock	Sim	No
24.	46ys;M;ATL-ca	8/17/2005	Sim	28 months	Alive		
25.	46ys;M;ATL-ca	5/30/2003	Sim	10 months	Septic Shock	Sim	No
26.	47ys;F;ATL-1-a	6/5/2006	Sim	16 months	Septic Shock	Sim	No
27.	48ys;F;ATL-a	4/25/2002	Sim	1 months	Septic Shock	Sim	No
28.	48ys;F;ATL-ca	4/24/2002	Sim	1 months	Septic Shock	Sim	No
29.	49ys;F;ATL-1-a*	1/2/2002	Não	1 day	Organic encephalopathy due to neoplastic infiltration + Hypercalcemia metabolic coma + Septic Shock	Sim	No
30.	57ys;F;ATL-a	2/15/2002	Sim	1 months	Septic Shock		No
31.	57ys;M;ATL-1-a	9/25/2003	Sim	7 days	Organic encephalopathy due to neoplastic infiltration + accute renal infection	Não	No
32.	58ys;M;ATL-a	11/12/1996	Sim	9 months (transferred to)			
33.	60ys;F;ATL-a	11/25/2003	Sim	2 months	Hyperleocostase with leokoestase incentral nervous system + pulmonary infection	Sim	No
34.	70 ys;F;ATL-a	7/5/2007	Não	2 days	Organic encephalopathy due to neoplastic infiltration + Hypercalcemia metabolic coma + Septic Shock	Sim	No
35.	72ys;M;ATL-c	5/29/2000	Sim	15 months	Hypercalcemia metabolic coma + Septic Shock	Sim	No
36.	83ys;F;ATL-c	6/15/1992	Sim+AZT+Inter- feron	60 months	Septic Shock	Sim	No
37.	91ys;F;ATL-ca	11/18/2003	Sim	34 months	Septic Shock	Sim	No

carried out [2]. Different regimes of cytotoxic chemotherapy have been employed to cure patients suffering from acute and immunosuppressant forms of ATL, however the rates of total response are less than 30% and there is a lack of durability in responses [13].

ATL being a major destructive hematological malignancy has a bad outcome, either it is acute or lymphoma type, with a survival time of 6 to 13 months [47]. According to Lymphoma Study Groups [22], the patient's survival rates were 24.3 month for the chronic type, 10.2 months for the lymphoma type and 6.2 months for the acute form, from a group of 854 individual patients**.** In a Brazilian study, in which 70 ATL cases were analyzed, the overall median survival time was 12 months [3]. Yet**,** we lay serious emphasis on the fact that in our study, lymphoma subtype group had the worst prognosis (median survival 1.0 month).

ATL commonly occurs in adults, as a minimum of 20-30 years after the inception of HTLV-I infection. The persons who have the disease transmitted in the childhood time, by vertical transmission, are more likely to be at a higher risk of getting the disease [1, 28]. It has been reported that the Brazilian patients are younger than the Japanese ones. In this study the average age was 42 years old, and it is similar to other regions of Brazil and from the Caribbean patients [3, 12, 32]. Though mostly ATL is accounted to affect patients in their fifties, in Japan [42], in the Jamaican and Brazilian series, the individuals are more likely to show the medical symptoms in the forth decade of their life [3, 4, 12, 32].

Amongst the HTLV-I-infected carriers the cumulative incidence of ATL, is approximated at 1-5% for both males and females in endemic areas [26]. In our series, 26 (70%) of the patients were female. Similar results were found in a survey conducted in central Brooklyn, which showed the yearly incidence of ATL was higher in females as compared to males (female-to-male ratio of 3:1) [21], however the disease is more common amongst men in Japan. Amongst the HTLV-I carriers in Japan, the cumulative incidence of ATL is approximated at 2.5%, with 1-2% in female and 3-5% in males [46].

In French Guiana, a greater incidence of ATL in blacks has been accounted [10] as well as in blacks with mulattos in Pernambuco and Bahia States in Brazil [3, 32]. In the present study the disease was also majorly found in non-white individuals (68%).

In case of adult HTLV-I infection, the development of ATL is highly unusual and merely periodic cases of sexual transmission and/or blood transfusion related HTLV-I transmission related with ATL have been found [6, 23, 24].

Although in our series four patients have history of blood transfusion before the diagnosis, it was not clearly the route of HTLV-I transmission. In spite of the fact that HTLV-I infection caused by blood transfusion is regarded as a significant danger for HAM/TSP, instances of post-transfusion ATL are extraordinary [1, 6, 33]. ATL and HAM/TSP are distinguished clinical conditions triggered by HTLV-I, and one or the other disease shows up independently in most patients. Although, few cases of connection are reported [3, 16, 19, 32]. In our study just one patient was found with this disease association.

The incidence of HTLV-I, reported annually, of related disease (ATL) has not been found in Brazil [32]. In addition, there are very few data available about the path of HTLV-I transmission among family settings of individuals with ATL in the region. Carvalho et al. [4] and Pombo-de-Oliveira [33], found a HTLV-I seroprevalence rate of 27, 5% and 36% respectively amongst the family members of individuals with ATL and in the present study 35, 8% of the relatives of ATL patients analyzed were HTLV-I seropositive.

According to the risk factors, in our study 12 patients were breast-fed by their mothers and among them 60% were HTLV-I positive and wet nurses breast fed four patients and their mothers were HTLV-I negative. These are in accordance with data found in Caribbean and Japanese cohort studies, where greater than 97% of mothers of ATL individuals were as well HTLV-I antibody-positive [1, 40].

In conclusion, our data emphasize the importance of the serologic test for HTLV-I antibodies, and specific immunophenotyping to differentiate ATL from other T-lymphoproliferative disorders. Alternatively, since ATL is majorly linked with HTLV-I infection in early years of life, transmitted by vertical route, it is very important to include in the prenatal routine the HTLV screening test and present the appropriate counseling to the seropositive pregnant women regarding to the breast-feeding, in order to brake the virus transmission cycle.

Acknowledgements

We would like to thank to Dr. Eleonora D'Avila Thomé for skin lesion picture, Dr. Renata Cravo and the staff of the Clinical Laboratory, Clinical Hematology and Hemoteraphy from HEMORIO for the contribution in this study.

List of Abreviation

ATL-a = adult T-cell leukemia acute subtype ATL-c = adult T-cell leukemia chronic subtype ATL- l = adult T-cell leukemia lymphoma subtype

ATL-ca = adult T-cell leukemia chronic evoluted to acute subtype ATL-la = adult T-cell leukemia lymphoma type evoluted to acute subtype

HAM/TSP – HTLV-I associated myelopathy/tropical spastic paraparesis

nd = not done

M = male

F = female

W = white

NW = non white

RJ = Rio de Janeiro state

HIV = human immunodeficiency virus

HPV = human papiloma virus

HBV = hepatitis B virus

HCV = hepatitis C virus

CNS = central nervous system

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