Adult T-Cell Leukemia/Lymphoma in Bahia, Brazil

Analysis of Prognostic Factors in a Group of 70 Patients

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Abstract

The purpose of this study was to evaluate whether subdivision of adult T-cell leukemia/lymphoma (ATL) on the basis of clinical types, skin involvement, histologic features, cell size, and proliferative index (PI) was clinically relevant. Skin lesions were present in 47 cases (67%). Five cases were classified as primary cutaneous tumoral (PCT) type not included in the Shimoyama classification and characterized by skin tumors and absence of systemic involvement, lymphocytosis, and hypercalcemia. Mortality was high (61/70 [87%]). The overall median survival time (MST) was 12 months. The following variables were adversely related to survival: acute, lymphoma, and PCT types; absence of skin lesions; large cells; and PI more than 18%. The longer MST observed in cases with skin lesions was probably due to prolonged survival of the smoldering type (58 months). The MST of the PCT type (21 months) was shorter than that of the smoldering type, confirming the importance of clearly defining these 2 types of ATL.

Adult T-cell leukemia/lymphoma (ATL) is an aggressive type of leukemia/lymphoma associated with the human T-cell lymphotropic virus type I (HTLV-I) that is characterized by a short survival time and a poor response to chemotherapy. In Brazil, the highest seroprevalence rate of HTLV-I in healthy subjects (1.8%) was observed in Salvador, a city of the state of Bahia,[1] situated on the northeastern coast of the country where the population is largely of African descent. In Rio de Janeiro, Brazil, 28.2% (53/188) of patients with T-cell malignancies had ATL.[2]

ATL has been classified into 4 clinical subtypes: acute, chronic, lymphoma, and smoldering **Table 1**.[3] Patients with acute and lymphoma types have a poor outlook with a median survival time (MST) of about 6 months for the acute type and 10 months for lymphoma. The chronic type has an MST of around 2 years. The MST in the smoldering type is quite variable, with some patients living for many years and others dying in less than a year.[3,4]

The morphologic appearance of ATL in tissue sections is highly variable and often mimics established pathologic subtypes of T-cell lymphomas not associated with HTLV-I. However, in the World Health Organization classification, all cases of leukemia/lymphoma associated with HTLV-I independent of the histologic pattern are classified as ATL,[5,6] not taking into consideration that this diagnosis can be made only after serologic or molecular studies because ATL has no specific histologic characteristics.[7] The pathologist, without knowing the serologic result, generally classifies HTLV-I–associated lymphomas as peripheral T-cell lymphoma, unspecified (PTCL-U) or other T-cell malignancies, such as mycosis fungoides (MF) or anaplastic large-cell lymphoma (ALCL).[8-11] PTCL-U corresponds to multiple morphologic

Table 1
Clinical Classification of Adult T-Cell Leukemia/Lymphoma*

Clinical Type	Lymphocytosis	LDH Level	Hypercalcemia	Organs Involved	Body Effusions
Smoldering	Absent	≤1.5 × N	Absent	Only skin and/or lungs and/or blood (≥5% of atypical lymphocytes in PB)†	Absent
Chronic	Present	≤2 × N	Absent	Any organ except bone, GIT, and CNS	Absent
Lymphoma	Absent	Variable	May be present	Lymph nodes† and any other organ	May be present
Acute	Present at high level	Usually high	Usually present	Any organ	Present
PCT	Absent	≤1.5 × N	Absent	Only skin	Absent

CNS, central nervous system; GIT, gastrointestinal tract; LDH, lactic dehydrogenase; N, normal upper limit; PB, peripheral blood; PCT, primary cutaneous tumoral type not included in the Shimoyama classification.
* Modified from the Shimoyama classification.
† Histologically proven tumor in lymph nodes is essential for classification.

subtypes of older classifications, including the pleomorphic T-cell lymphoma.[12] These diverse histologic patterns have not been taken into consideration in the Shimoyama classification,[3] and it would be interesting to evaluate whether they are related to clinical type and prognosis.

In the present study, the clinicopathologic and immunophenotypic features of 70 cases of ATL were evaluated. The purposes of the study were as follows: (1) study whether the clinical types defined in the Shimoyama classification are related to prognosis and evolution of the disease in Brazilian patients; (2) investigate whether other parameters besides those included in the Shimoyama classification, such as the presence or absence of skin lesions, cell size, and the degree of proliferative index (PI), are also related to evolution and prognosis; and (3) determine whether there is a relationship between the histologic patterns and Shimoyama clinical types and prognosis.

Materials and Methods

We reviewed 67 cases of HTLV-I–associated lymphoma/leukemia referred to the Pathology Department, Federal University of Bahia Teaching Hospital for diagnosis by histopathology or immunohistochemistry between 1991 and August 2006. We included 3 other cases that were diagnosed hematologically. Cases with concomitant seropositivity for HIV and cases in which status was unknown owing to incomplete follow-up were excluded. Clinical data were collected from the patient records and included the results of physical examination, blood cell counts, chest radiography, abdominal ultrasonography, thoracic and abdominal tomography, blood levels of calcium and lactate dehydrogenase, and examination of bone marrow aspirate and/or biopsy. Survival intervals were calculated as the date of diagnosis to the date of the last follow-up or death (cutoff date, November 2006). Clinical subtypes were classified according to the Shimoyama criteria.

All patients were serologically positive for HTLV-I (according to enzyme-linked immunosorbent assay with confirmation by Western blot). Diagnosis was based on positive serologic findings and a histologically and/or cytologically proven diagnosis of leukemia/lymphoma of peripheral T-cell origin. In cases with prolonged survival, analysis of clonality using Southern blot, inverse polymerase chain reaction,[13] or long-inverse polymerase chain reaction[14] was performed. Therapy varied: chemotherapy alone, interferon-alfa associated with zidovudine, or chemotherapy alternated with interferon-alfa plus zidovudine. Radiotherapy was used in some smoldering cases with more infiltrated lesions and in the primary cutaneous tumoral type to reduce the tumors, in association with other treatments. Treatment with psoralen-UV-A was used in smoldering cases with disseminated lesions.

Histopathologic and Immunohistochemical Studies

Except for 3 cases in which diagnosis was exclusively hematologic, all other patients had undergone biopsies of skin lesions, lymph nodes, or both. Autopsies were performed in 5 cases, and all organs were examined histologically. Histologic sections were seen by 2 pathologists (A.L.B. and H.S.B.), and the cases were classified morphologically according to the World Health Organization classification of leukemias/lymphomas.[5]

An immunohistochemical study of the neoplastic cells was performed on formalin-fixed, paraffin-embedded sections using a panel of antibodies and a standard streptavidin-biotin-peroxidase technique.[15] The following immunocytochemical markers were used: CD45RO (OPD4 and/or UCHL-1), CD3, CD4, CD5, CD7, CD8, CD20, CD25, CD30, ALK-1, and CD79a. The PI was evaluated using Ki-67. With the exception of CD4, CD5, and CD25, which were purchased from Novocastra, Newcastle upon Tyne, England, all other antibodies were obtained from DakoCytomation, Glostrup, Denmark. Some of the cases included in this series have been described in previous articles.[4,7,8,16]

The protocol of the present study was approved by the institutional review board of the Federal University of Bahia Teaching Hospital. Informed consent was obtained in all cases.

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Statistical Analysis

Univariate analysis was carried out to examine the association between each variable and progression to death. The variables analyzed for prognostic value were clinical subtypes, presence or absence of skin lesions, histopathologic diagnosis, the size of the cells (small and/or medium vs large), and a PI of 18% or less or more than 18%). The Kaplan-Meier method was used to estimate the cumulative probability of patient survival over time. Comparison of different curves according to subgroups was carried out using the generalized Wilcoxon test.

Results

Clinical Features

The clinical features are summarized in **Table 2**. Of 70 cases, 5 (7%) could not be classified according to the Shimoyama criteria and were considered cases of the primary cutaneous tumoral type that is characterized by the presence of cutaneous tumors **Image 1**; absence of lymphadenomegaly, lymphocytosis, hypercalcemia, and involvement of internal organs; and normal or slightly elevated lactate dehydrogenase levels. During evolution, 3 cases of the smoldering type evolved to acute, chronic, and primary cutaneous tumoral types. In 47 cases (67%), there was skin involvement, and in 24 of these cases (smoldering and primary cutaneous tumoral), the lesions began in the skin and remained in the skin for at least 6 months following diagnosis. All cases of the smoldering type and 9 (90%) of 10 cases of the chronic type included skin involvement at diagnosis. Among the 9 living patients, all with active disease, 7 had disease of the smoldering type, 1 had chronic type, and 1 had the primary cutaneous tumoral type.

Around 50% of patients (37 cases) had a survival time of 1 year or less; 22 patients lived longer than 1 year, and 11 lived for 5 years or more. In all cases in which survival time was longer than 5 years, monoclonal virus integration was confirmed. The patient with the longest survival time (14 years) is still alive and has the smoldering form of the disease.[16] The disease was the cause of death in 46 cases, and 15 cases were due to infection or other causes unrelated directly to ATL.

Histopathologic and Immunohistochemical Features

The frequency of the histologic/hematologic diagnosis and its correlation with the different clinical types is shown in **Table 3**. Of 47 classified as PTCL-U **Image 2**, 29 were of the more aggressive clinical types (acute and lymphoma); 14 of 16 cases of MF **Image 3** corresponded to the smoldering and chronic types, less aggressive types; 3 of 4 cases of ALCL **Image 4** manifested clinically as the lymphoma type and 1 as the smoldering type. Large cells were present in 18 of 47 cases of PTCL-U and all cases of ALCL. With the exception of 2 cases of the chronic and 1 of the smoldering type, all the other cases with large cells corresponded to the acute, lymphoma, and primary cutaneous tumoral types.

The immunophenotype most frequently observed was CD3+/CD5+/CD45RO+/CD7–/CD20–, CD79a–. CD25 was positive in 42 of 45 cases, CD4+ in 42 of 64, and CD8+ in 13 of 64 cases. CD30 was positive in only 6 of 63 cases, including the 4 ALCL cases. In the ALCL cases, the phenotype was CD3+ and/or CD45RO+/CD20–/CD79a–/CD30+. ALK-1

Table 2
Clinical Data for 70 Cases of Adult T-Cell Leukemia/Lymphoma*

Characteristic	Result
Mean age (range, y)	48.6 (9-84)
Age ≤18 y	4 (6)
Male/female ratio	36:34
Race	
African descendents	61 (87%)
Whites	9 (13)
Association with HAM/TSP	10 (14)
Clinical type	
Smoldering	19 (27)
Acute	19 (27)
Lymphoma	17 (24)
Chronic	10 (14)
Primary cutaneous tumoral†	5 (7)

HAM/TSP, myelopathy associated with human T-lymphotropic virus-I/tropical spastic paraparesis.
* Data are given as number (percentage) unless otherwise indicated.
† Not included in the Shimoyama classification.

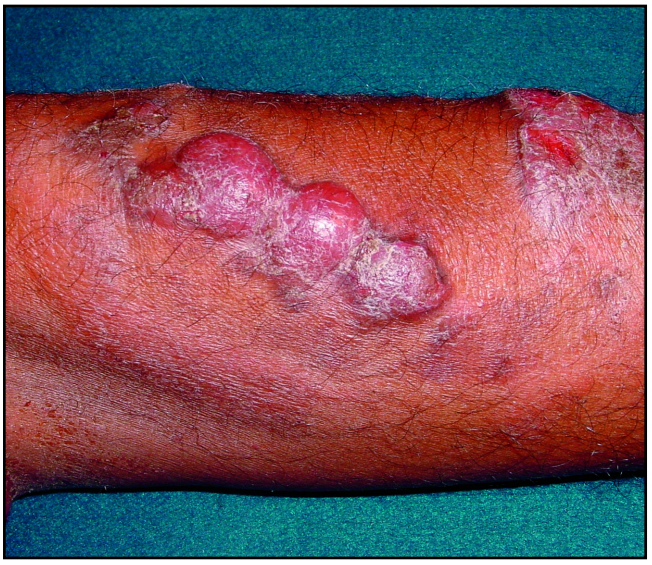

Image 1 Primary cutaneous tumoral clinical type of adult T-cell leukemia/lymphoma. Autopsy did not reveal any other involvement besides the skin. Human T-lymphotropic virus-I monoclonal integration was detected in peripheral blood mononuclear cells.

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Table 3
Clinical Types of Adult T-Cell Leukemia/Lymphoma Correlated With Histologic/Hematologic Diagnoses

		Leukemias/Lymphomas			
Clinical Type	**No. (%) of Cases**	**PTCL-U**	**MF**	**ALCL**	**Leukemia***
Smoldering	19 (27)	8	10	1	0
Acute	19 (27)	16	0	0	3
Lymphoma	17 (24)	13	1	3	0
Chronic	10 (14)	6	4	0	0
PC tumoral	5 (7)	4	1	0	0
Total	70	47	16	4	3

ALCL, anaplastic large cell lymphoma; MF, mycosis fungoides; PC, primary cutaneous; PTCL-U, peripheral T-cell lymphoma, unspecified.
* Acute cases with hematologic diagnosis.

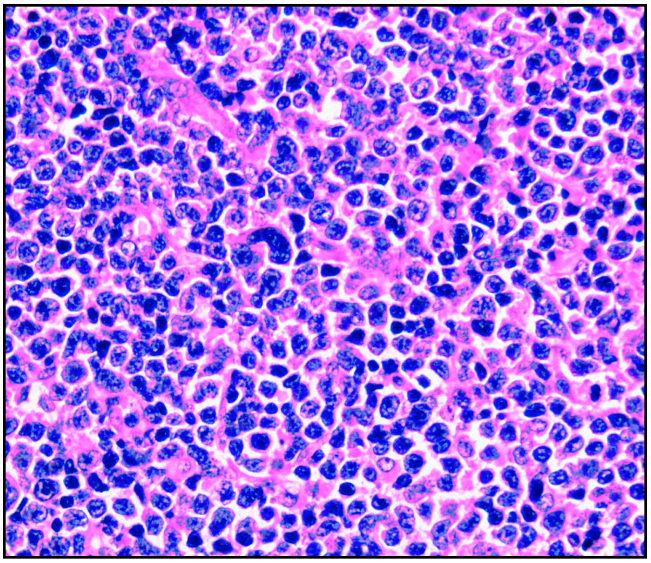

Image 2 Peripheral T-cell lymphoma, unspecified. Lymph node diffusely infiltrated by pleomorphic medium and large cells (H&E, ×250).

was negative in the 3 cases of ALCL in which it was tested. The PI was evaluated in 53 cases (11 lymphoma type, 12 acute, 10 chronic, 15 smoldering, and all cutaneous tumoral) and was found to be more than 18% in 28 (53%) of all cases: in 10 (91%) of 11 cases of the lymphoma type, 4 (80%) of 5 of the primary cutaneous tumoral type, 9 (75%) of 12 of the acute type, 4 (40%) of 10 of the chronic type, and 1 (7%) of 15 of the smoldering type. The case of the smoldering type with a PI of more than 18% corresponded histologically to ALCL.

Evaluation of Survival

The MST was 12 months (95% CI, 6.54-17.46 months). A more marked fall in survival was observed within 18 months following diagnosis, after which there was a gradual reduction in survival **Figure 1**. The survival curves for the different clinical forms are shown in **Figure 2**. The longest survival time was seen in the smoldering type and the shortest

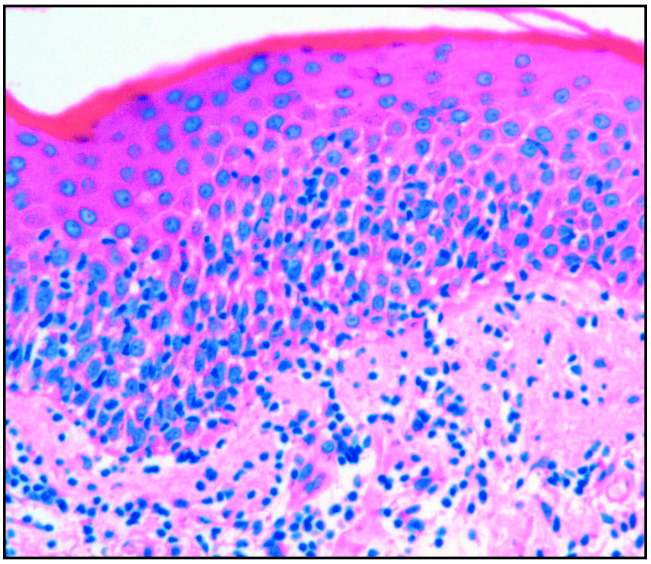

Image 3 Mycosis fungoides. Atypical and irregular small lymphocytes in the upper dermis with epidermotropism (H&E, ×200).

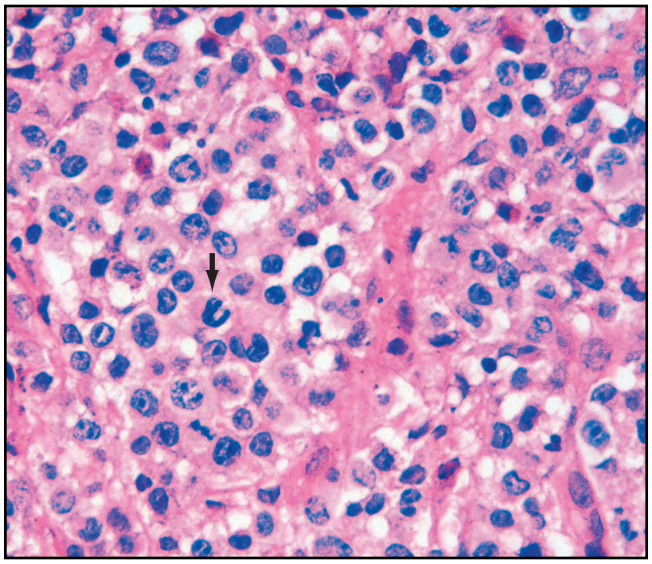

Image 4 Anaplastic large cell lymphoma. Lymph node architecture obliterated by densely packed large cells with abundant cytoplasm. The arrow shows a horseshoe-shaped nucleus (H&E, ×400).

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in the acute type **Table 4**. A statistically significant difference was found in the MST between the different clinical types ($P < .01$). When the cases were analyzed according to the presence or absence of skin lesions, strong evidence was found for a difference in MST between these 2 groups ($P < .010$), with a longer MST in the group with skin lesions. However, in the acute clinical type, the MST was higher in patients without skin lesions **Table 5**. The MSTs for the pathologic diagnoses were as follows: MF, 45 months; PTCL-U, 9 months; and ALCL, 7 months; the MST for the leukemic cases hematologically diagnosed was 21 months. There were no statistically significant differences in survival between pathologic diagnoses ($P = .279$), although the cases with MF-like morphologic features had a longer survival time compared with cases in the other diagnostic groups. The MST in cases with large cell morphologic features was shorter than in the cases with small and/or medium cells ($P = .045$) **Figure 3**. The MST in cases with a PI of more than 18% was shorter than in the cases with a PI of 18% or less ($P = .003$) **Figure 4**.

Discussion

ATL is generally reported in adults, the mean age of onset around 58 years,[3,17] but rare cases have been described in children and adolescents.[18] As previously observed, ATL appears earlier in Brazil than in Japan.[2,8] In the present study, the mean age of patients at diagnosis was 48.6 years, and 4 cases occurred in childhood or adolescence. An interesting aspect was the finding of an association with myelopathy associated

Table 4
Mean and Median Survival According to Clinical Type of Adult T-Cell Leukemia/Lymphoma

Clinical Type	Mean (95% CI), mo	Median (95% CI), mo
Smoldering	77.83 (45.16-110.50)	58.00 (45.17-70.83)
Acute	8.06 (1.76-14.36)	4.00 (1.6-6.4)
Lymphoma	19.94 (5.61-34.27)	9.00 (4.16-13.84)
Chronic	30.96 (13.26-48.66)	18.00 (0.95-35.04)
PC tumoral	20.10 (13.62-26.60)	21.00 (11.64-30.36)
Overall	33.85 (22.27-45.42)	12.00 (6.54-17.46)

CI, confidence interval; PC, primary cutaneous.

Table 5
Mean and Median Survival According to the Presence or Absence of Skin Lesions in Clinical Types of Adult T-Cell Leukemia/Lymphoma

Clinical Type	Mean (95% CI), mo	Median (95% CI), mo
With skin lesions*		
Smoldering	77.83 (45.16-110.50)	58.00 (45.20-70.83)
Acute	5.67 (1.72-9.61)	4.00 (0.00-9.84)
Lymphoma	15.33 (5.35-25.31)	12.00 (2.40-21.60)
Chronic	33.18 (13.97-52.39)	22.00 (10.31-33.69)
Primary cutaneous tumoral	20.10 (13.62-26.58)	21.00 (11.64-30.36)
Overall	42.85 (26.40-59.29)	20.00 (10.58-29.42)
Without skin lesions		
Acute	11.02 (0.00-22.50)	6.00 (0.00-13.59)
Lymphoma	22.46 (0.68-44.23)	7.00 (3.76-10.24)
Overall	16.54 (5.03-28.12)	6.00 (4.12-7.88)

* All smoldering and primary cutaneous tumoral and 90% of chronic cases had skin lesions.

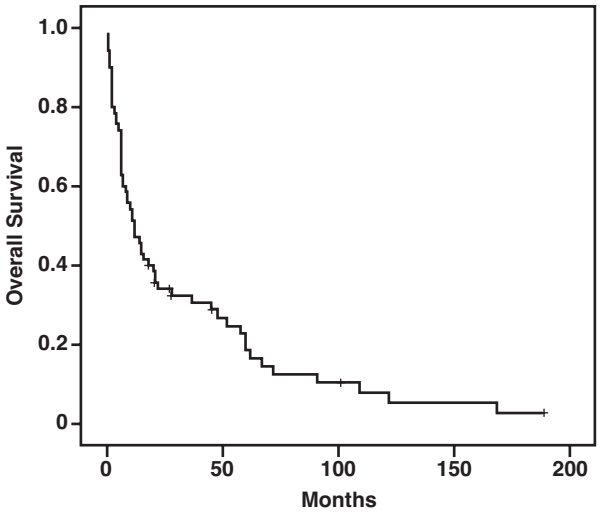

Figure 1 Overall survival curve for 70 cases of adult T-cell leukemia/lymphoma.

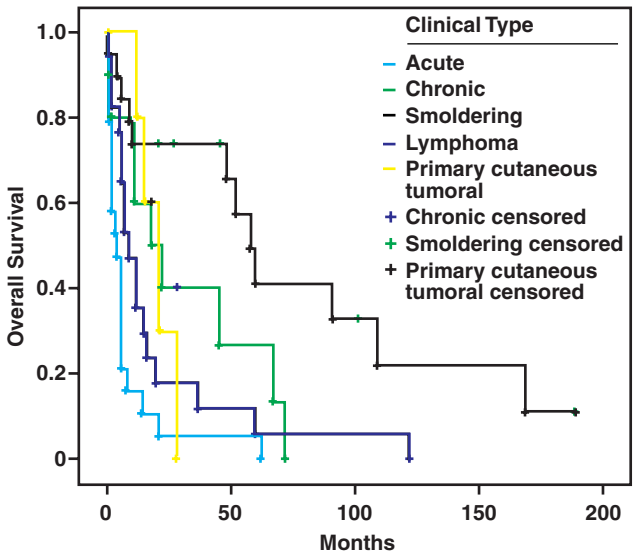

Figure 2 Survival curves for patients with adult T-cell leukemia/lymphoma according to clinical type.

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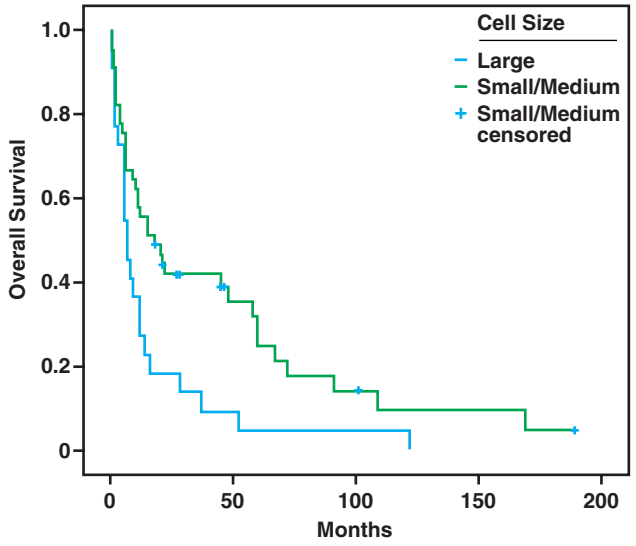

Figure 3 Survival curves in cases with small or medium cells compared with cases with large cells.

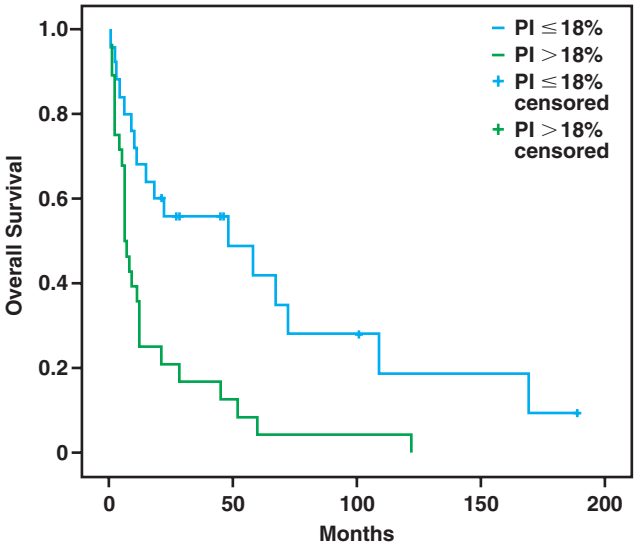

Figure 4 Survival curves of groups with a proliferative index (PI) of 18% or less and with a PI of more than 18%.

with HTLV-I/tropical spastic paraparesis (HAM/TSP) in 14% of the cases. The association of HAM/TSP and ATL, which have distinct pathogeneses, is considered rare.[19]

The different clinical types of ATL commonly involve the skin, the incidence varying from 43% to 72%.[20] In the present study, skin involvement was present in 67% of cases, including all of the smoldering cases and 90% of the chronic cases.

In 1992, almost immediately after Shimoyama had classified the clinical types of ATL, Johno et al[21] described a different clinical type, which they referred to as cutaneous ATL, in which lesions were restricted to the skin. They further subdivided this cutaneous ATL type into tumoral and erythematopapular subtypes and reported that the tumoral subtype had a poorer prognosis. According to our observations, the erythematopapular subtype described by these authors corresponds, in fact, to Shimoyama's smoldering ATL, and only the primary cutaneous tumoral subtype constitutes a distinct clinical form of the disease with a poor prognosis. In the present study, 5 cases of cutaneous tumors and no involvement of internal organs, lymphadenomegaly, lymphocytosis, or hypercalcemia could not be classified into any of the Shimoyama clinical types and were defined as the primary cutaneous tumoral type of ATL. Based on these findings, we suggest the inclusion of a new clinical type of ATL, primary cutaneous tumoral, with the characteristics described herein.

As expected, lethality was very high, with only 13% of patients still alive at last follow-up, the majority of whom had the smoldering form of the disease. The following variables were adversely related to survival: acute, lymphoma, and primary tumoral cutaneous clinical types; absence of skin involvement; large cell morphologic features; and a PI of more than 18%.

The acute, lymphoma, and primary cutaneous tumoral types had a shorter MST. The overall MST (12 months) and the MST observed in the acute, lymphoma, and chronic types were not very different from those found in Japan.3 However, among patients in Kagoshima (Japan),[22] the MST for the smoldering type with skin lesions (16 months) is much shorter than the MST observed in the present study (58 months). Therefore, the prognosis for the smoldering type in our population seems to be much better than in Kagoshima.

In the present study, the MST of the primary tumoral cutaneous type (21.0 months) was much shorter than the MST of the smoldering type (58.0 months). This finding stresses the importance of separating these 2 types of primary cutaneous ATL.

A longer MST was observed in the group with skin lesions, which included all patients with the smoldering type and 90% with the chronic type. Considering that the smoldering type has the longest MST, this fact may explain, at least in part, the shorter MST in the group with no skin lesions.

According to Matutes and Catovsky,[23] lack of skin lesions is considered an adverse prognostic factor influencing survival. However, Ishida et al[24] did not find a significant difference in the overall survival between cases with or without skin involvement. In their study, there was a marked predominance of the acute clinical type (75.5%) and only 5% of the smoldering type, which may explain these results. We believe that in smoldering ATL, the better outcome is not related to the presence of skin lesions but to the absence of visceral involvement and leukemia. In the other clinical types, it is not the skin lesions that are responsible for the poor prognosis, but the presence of leukemia and/or visceral involvement.

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The most frequent histopathologic diagnosis observed in the present series was PTCL-U, but patterns compatible with MF and ALCL have also been seen. MF was frequently associated with smoldering and chronic types, whereas PTCL-U was frequently associated with the more aggressive types, acute, lymphoma, and primary cutaneous tumoral. The only smoldering case that corresponded histologically to an ALCL had a prolonged survival time (56 months). Survival was longer in MF cases, but the difference was not statistically significant. The better prognosis in cases of MF correlates with the small size of the cells in this morphologic category.

Large cell size and a PI of more than 18% correlated with shorter survival time. With the exception of 2 cases of the chronic and 1 of the smoldering type, all other cases with large cells corresponded to the more aggressive clinical types. The case of smoldering type with large cells had a diagnosis of ALCL. This lymphoma, when primary of the skin and HTLV-I–, has a better prognosis despite large cells and a high PI.[25]

The importance of PI in the prognosis of ATL has only been evaluated in peripheral blood T lymphocytes.[26] Shirono et al[26] proposed a new classification of clinical stages of ATL based on low-positive cases with fewer than 18% Ki-67+ cells and high-positive cases with more than 18% Ki-67+ cells. These investigators reported that prognosis in the latter group was poorer. By evaluating PI using immunohistochemical analysis, we found a statistically significant difference in the MST between these 2 groups: cases with 18% or fewer Ki-67+ cells and those with more than 18% of these cells. The latter group had a shorter MST. Because a correlation was observed between an elevated PI and the more aggressive clinical types such as acute, lymphoma, and primary cutaneous tumoral, we believe that this new classification based only on PI would not add much to the Shimoyama clinical classification.

Except for the CD8 positivity seen in 13 cases, the phenotype in all cases was that typically observed in ATL, ie, CD3+/CD5+/OPD4+/CD25+/CD7–/CD20–/CD79a–.[6] CD8 positivity has infrequently been observed in ATL.[27-29] Ohshima et al[29] consider that CD8 positivity possibly constitutes an aberrant surface marker in ATL.

The best prognoses were observed in the smoldering and chronic clinical types, in tumors with small and/or medium cells, and in cases with a low PI and a histologic pattern of MF. Except for the acute leukemic type of ATL, which is usually diagnosed by hematopathologists, the first diagnosis of lymphoma in ATL is performed by pathologists in a tissue biopsy specimen. Thus, it is important that in endemic areas for HTLV-I, these professionals be aware that ATL, besides manifesting histologically as PTCL-U, may also resemble MF or ALCL and that HTLV-I infection should be investigated in these T-cell lymphomas.

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