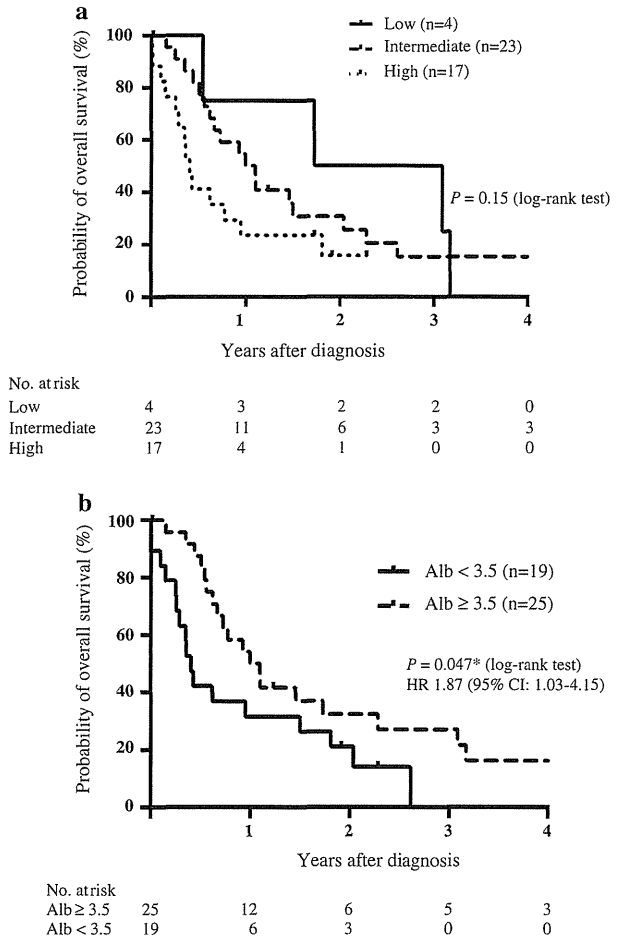

Fig. 4 Survival of elderly patients. **a** Survival according to the simplified ATL-prognostic index (PI). **b** Survival according to Albumin (Alb)

significantly lower in patients with a lower Alb level [≥3.5 (n = 25) vs <3.5 g/dL (n = 19); P = 0.047; log-rank test] (Fig. 4b). However, other factors, such as stage [I, II (n = 5) vs. III, IV (n = 39); P = 0.45], PS [0, 1 (n = 21) vs. 2–4 (n = 23); P = 0.29], and sIL-2R [≤20,000 (n = 29) vs. >20,000 U/mL (n = 15); P = 0.058] did not significantly affect OS.

Discussion

In this retrospective study, we showed the treatment outcome of elderly patients with aggressive ATL. In our hospital, the median ages of patients with aggressive ATL at diagnosis were 61 years between 1994 and 2000 (range 33–84 years) and 65 years between 2001 and 2010 (range 35–85 years). The rate of patients 70 years or older was 16 % (9 out of 57) in the former period and 36 % (45 out of 126) in the latter period (Fig. 5). The age of ATL patients has increased over time in our hospital, similar to the tendency observed in a nationwide survey [14]. Therefore, the best way to treat elderly ATL patients has become a very important issue.

The VCAP-AMP-VECP regimen has been reported to be more likely to benefit younger patients, because no difference was detected in the outcome between patients ≥56 years old treated with VCAP-AMP-VECP and those treated with CHOP-14 [9]. In our study, for patients treated with VCAP-AMP-VECP, MST and OS at 2 years were almost identical to these results in patients ≥56 years old but under 70 years old in a clinical trial [9]. On the other hand, those who received another treatment as the first choice had a poorer prognosis. Selection bias was included

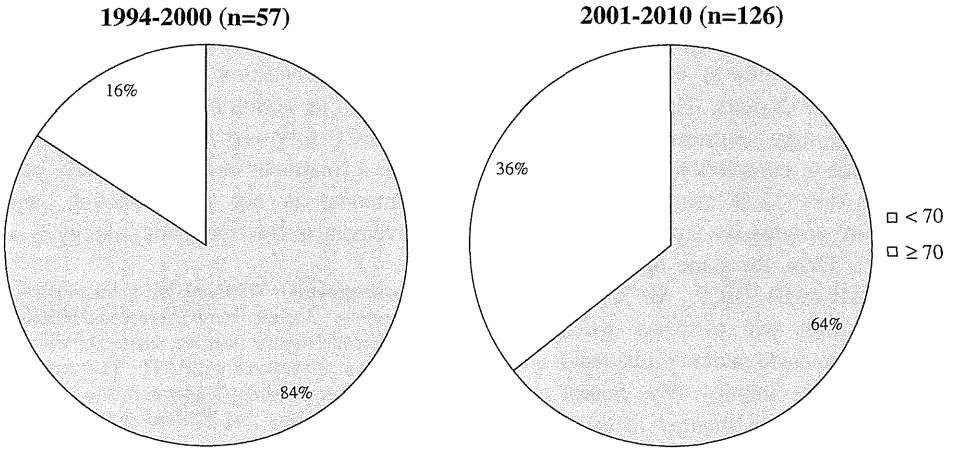

Fig. 5 Age distribution of the patients with aggressive ATL at diagnosis

in the choice of treatment in this retrospective study. Patients treated with chemotherapy other than VCAP-AMP-VECP were older ($P = 0.02$; Mann–Whitney U test) and may have been in worse condition. In addition, patients who did not complete first cycle of VCAP-AMP-VECP were excluded from VCAP-AMP-VECP group in this retrospective analysis, and patients who became treatment-resistant extremely early after the start of chemotherapy may not have been included in the VCAP-AMP-VECP group. Thus, we cannot conclude the superiority of VCAP-AMP-VECP compared to other regimens. However, our result suggests that a nearly identical outcome to the younger patients may be expected in elderly patients receiving a VCAP-AMP-VECP-like regimen if they are in relatively good condition. Dose adjustment may be required for the VCAP-AMP-VECP-like regimen when treating elderly patients to reduce the adverse events, because hematologic toxicity and infections were reported more frequently with the VCAP-AMP-VECP regimen than with CHOP-14. Indeed, only 8.8 % (3/34) of elderly patients were treated with a full dose of VCAP-AMP-VECP as the initial treatment in our study. The degree of dose reduction varied, and the doses were reduced to about half to 80 % in most cases according to the patients' condition.

We should keep in mind that two-fifths of elderly patients were not candidates for an intensive treatment such as VCAP-AMP-VECP, even in our university hospital. The ratio of elderly patients with a worse general condition who were not candidates for this intensive regimen may be higher at the local public hospital. Thus, further improvement in the treatment strategy for elderly ATL patients is required.

The total number of cycles of VCAP-AMP-VECP that constituted a complete treatment was defined as six or seven in the clinical study [8, 9]. In our study, only six out of 32 patients (19 %) completed six cycles of VCAP-AMP-VECP, although some patients were treated with maintenance therapy as described below. Three of the patients who completed six cycles of the VCAP-AMP-VECP regimen survived over 2 years. Thus, continuation of intensive chemotherapy may contribute to prolonged survival. However, the rate of completion of six cycles of VCAP-AMP-VECP was only 32 % even in the clinical study, mainly because of progressive cytopenia and PD during the treatment [9]. Thus, for some elderly patients who responded to VCAP-AMP-VECP, we stopped the intensive chemotherapy after two or three cycles and orally treated them with etoposide and/or sobuzoxane and/or prednisone as maintenance therapy. We cannot conclude the efficacy of maintenance therapy in this study, because the number of patients was not sufficient, and the background may be heterogeneous for patients treated with such a strategy. However, our results appeared to be acceptable, and such a treatment strategy may become an option with an emphasis on quality of life of elderly patients. Further examination is expected to confirm the efficacy of maintenance therapy.

Most elderly patients included in this study were at intermediate or high risk in the ATL-PI, which suggests that our study did not inadvertently select patients with a better disease status. We could not show a significant difference in prognosis with the ATL-PI in our patients. The number of patients may have been too small to analyze the efficacy of the prognostic index. Furthermore, low-risk patients were rare among the elderly patients in our study. The fact that older age itself is included as a risk factor in the ATL-PI may be the main reason for the deviation in the risk group.

The efficacy of mogamulizumab, a humanized anti-CC chemokine receptor 4 antibody, as a single agent has been reported for relapsed ATL [17]. Mogamulizumab is now available in clinical practice for relapsed refractory ATL patients in Japan. Thus, for example, administration of mogamulizumab for maintenance therapy may prevent relapse or regrowth of the disease. On the other hand, a clinical trial for mogamulizumab combined with VCAP-AMP-VECP as the initial treatment for aggressive ATL has been performed, although the result has not been published yet. Thus, mogamulizumab with dose-reduced VCAP-AMP-VECP or a less-toxic regimen as the initial treatment may become a treatment option for elderly patients with aggressive ATL in the near future. An appropriate clinical trial is warranted to reveal the efficacy of such an approach. However, a prospective clinical trial may be difficult in elderly patients with aggressive ATL. In this report, no patient was treated with mogamulizumab, and our results provide a basis for the treatment result in elderly patients before the introduction of antibody therapy for the treatment of ATL.

In conclusion, our results suggest that dose-modified VCAP-AMP-VECP may become an optional regimen for the treatment of elderly patients with aggressive ATL if their general condition is good enough for intensive chemotherapy. In addition, two or three cycles of VCAP-AMP-VECP followed by maintenance therapy may also become a treatment option for elderly patients. However, the outcome is not good enough, and thus, further improvement in the treatment strategy is warranted.

Acknowledgments We thank the hematologists in the Department of Hematology, Atomic Bomb Disease and Hibakusha Medicine Unit, Atomic Bomb Disease Institute, Nagasaki University, for diagnosis and treatment of patients with ATL. This work was supported by a grant for cancer research (H23-gan rinsho-ippan-022) from the Ministry of Health, Labor and Welfare of Japan.

Conflict of interest The authors declare that they have no conflict of interest.

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Biol Blood Marrow Transplant 20 (2014) 1968–1974

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Treatment of Patients with Adult T Cell Leukemia/Lymphoma with Cord Blood Transplantation: A Japanese Nationwide Retrospective Survey

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Article history:
Received 9 June 2014
Accepted 12 August 2014

Key Words:
Adult T cell leukemia/lymphoma (ATL)
Cord blood transplantation
Graft-versus-adult T cell leukemia/lymphoma

A B S T R A C T

Allogeneic bone marrow and peripheral blood stem cell transplantations are curative treatment modalities for adult T cell leukemia/lymphoma (ATLL) because of the intrinsic graft-versus-ATLL effect. However, limited information is available regarding whether cord blood transplantation (CBT) induces a curative graft-versus-ATLL effect against aggressive ATLL. To evaluate the effect of CBT against ATLL, we retrospectively analyzed data from 175 patients with ATLL who initially underwent single-unit CBT. The 2-year overall survival (OS) rate was 20.6% (95% confidence interval [CI], 13.8% to 27.4%). A multivariate analysis revealed that the development of graft-versus-host disease (GVHD) was a favorable prognostic factor for OS (hazard ratio, .10; 95% CI, .01 to .94; $P = .044$). Furthermore, the 2-year OS (42.7%; 95% CI, 28.1% to 56.6%) of patients with grade 1 to 2 acute GVHD was higher than that of patients without acute GVHD (24.2%; 95% CI, 11.2% to 39.8%; $P = .048$). However, the cumulative incidence of treatment-related mortality (TRM) was high (46.1%; 95% CI, 38.2% to 53.7%), and early death was particularly problematic. In conclusion, CBT cures patients with ATLL partly through a graft-versus-ATLL effect. However, novel interventions will be required, particularly in the early phase, to reduce TRM and optimize GVHD.

INTRODUCTION

Adult T cell leukemia/lymphoma (ATLL), an aggressive peripheral T cell neoplasm caused by the human T cell lymphotropic/leukemia virus type-1, has an extremely poor prognosis [1]. Intensive chemotherapy and autologous stem cell transplantation have not been shown to improve this prognosis [2,3]. As a curative treatment, allogeneic hematopoietic stem cell transplantation (allo-HSCT) can confer long-term remission via a graft-versus-ATLL effect in a proportion of patients with ATLL [4-7]. Recent reports have demonstrated that allo-HSCT using bone marrow (BM) or peripheral blood stem cells (PBSC) from a related or unrelated donor can effectively treat ATLL, yielding a 3-year overall survival rate

Financial disclosure: See Acknowledgments on page 1973.

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http://dx.doi.org/10.1016/j.bbmt.2014.08.012
1083-8791/

(OS) of approximately 30% [8-16]. However, patients with ATLL typically lack a suitable HLA-identical sibling donor because both the recipients and donors are typically elderly and because the aggressive ATLL tumor burden reduces the available time to find a suitable unrelated donor within the Japan Marrow Donor Program. Umbilical cord blood, which can serve as an alternative to BM or PBSC as a source of stem cells, has been used primarily to treat children; however, the number of unrelated-donor cord blood transplantation (CBT) procedures used to treat adult patients with ATLL is increasing in Japan. The rapid availability of CBT may provide a great advantage for patients who require urgent allo-HSCT to treat aggressive ATLL [17].

Currently, the outcome of CBT in patients with acute leukemia is comparable to that of other graft sources [18,19]; however, there are few reports on the outcomes of CBT in patients with ATL [20,21]. Moreover, it is difficult to draw firm conclusions regarding the efficacy of this procedure because of the small number of cases. Therefore, to evaluate the role of CBT for ATLL in a larger and more recent cohort, we performed a nationwide retrospective study of patients with ATLL who underwent CBT as the initial allo-HSCT.

PATIENTS AND METHODS

Data Collection

We analyzed nationwide survey data from the Japan Society for Hematopoietic Cell Transplantation regarding patients with ATLL who had undergone an initial CBT between March 2001 and December 2009 (n = 175). This analysis included the patients' clinical characteristics, such as the age at transplantation, gender, disease status at transplantation, date of transplantation, time from diagnosis to transplantation, conditioning regimens, and number of infused cells. The number of mismatches was counted with respect to HLA-A, HLA-B (low-resolution typing), and DRB1 (high-resolution typing). The present study was approved by the data management committees of the Japan Society for Hematopoietic Cell Transplantation as well as the institutional ethics committee of the Kyushu University Graduate School of Medical Sciences.

Definitions

OS was defined as the time from transplantation until death, and patients who remained alive at the time of the last follow-up were censored. The causes of death were reviewed and categorized as either ATLL-related or transplantation-related mortality (TRM). *ATLL-related mortality* was defined as death caused by a relapse or progression of ATLL, whereas *TRM* was defined as any death related to transplantation other than ATLL-related mortality, according to the judgment of each institution. The patients were divided into 2 groups according to the conditioning regimen: full-intensity conditioning (FIC) and reduced-intensity conditioning (RIC). FIC and RIC were defined according to the proposals of Giralt et al. [22] and Bacigalupo et al. [23], respectively, with slight modifications. In the present study, conditioning regimens that included ≥5 Gy of total body irradiation (TBI) in a single fraction or ≥8 Gy of TBI in multiple fractions, oral busulfan (BU) at >8 mg/kg, intravenous BU at >6.4 mg/kg, or melphalan (Mel) at >140 mg/m^2 were considered FIC; all others were classified as RIC.

Statistical Analysis

Descriptive statistics were used to summarize the variables related to patient demographics and transplantation characteristics. The probability of the OS time was estimated according to the Kaplan-Meier method. To evaluate the influences of confounding factors on acute graft-versus-host disease (GVHD) and survival, the log-rank test and proportional hazards modeling were used for the univariate and multivariate analyses, respectively. The Cox proportional hazard model was used for the multivariate analyses of OS in which all independent variables were incorporated in the model, followed by the use of a stepwise selection method [24]. Fine and Gray proportional hazard modeling was used to estimate the effects of the same variables used in the multivariate analysis for OS on the cumulative incidence rates of TRM and ATLL-related mortality [25,26]. In these regression models, the occurrence of GVHD was treated as a time-dependent covariate [27]. In the analysis of acute GVHD, patients were assigned to the "no acute GVHD group" at the time of transplantation and transferred to the "acute GVHD group" at the onset of the maximum grade of acute GVHD. The landmark method was used to evaluate the effects of GVHD on OS and the cumulative incidence of disease-associated and treatment-related deaths among patients who remained alive at 60 days for acute GVHD and at 100 days for chronic GVHD after transplantation. Factors associated with at least borderline significance ($P \leq .10$) in the univariate analysis were subjected to a multivariate analysis using a backward stepwise covariate selection. All P values were 2-tailed, and P values ≤.05 were considered statistically significant. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University), a graphical user interface for R (The R Foundation for Statistical Computing, version 2.13.0) [28].

RESULTS

Patient Characteristics

The characteristics of 175 ATLL patients who received a single CBT are shown in Table 1. The median age at CBT was 55 years (range, 27 to 79 years). The cohort comprised 70 women and 105 men with the following ATLL statuses at CBT: complete remission (CR; n = 50), not in CR (n = 116), and unknown (n = 9). The conditioning regimen intensity was classified as FIC in 63 (36%) patients and RIC in 128 (62%) patients. FIC was further subdivided into 2 groups as follows: TBI (n = 47) or non-TBI (n = 15). RIC was also subdivided into 3 groups as follows: fludarabine (Flu) + Mel (n = 75), Flu + BU (n = 15), and other types (n = 15). Cyclosporine and tacrolimus were administered for prophylaxis to 90 (51%) and 77 patients (44%), respectively. Cyclosporine-based prophylaxis was subdivided into 3 groups as follows: (1) cyclosporine

Table 1
Patient Characteristics at Cord Blood Transplantation

Variables	No. of Patients (n = 175)
Age at transplantation, median (range), yr	55 (27-79)
Gender	
Male	105
Female	70
Disease status at transplantation	
CR	50
Not in CR	116
Unknown	9
Conditioning regimen	
FIC	63
RIC	108
Unknown	4
GVHD prophylaxis	
Cyclosporine-based	90
Tacrolimus-based	77
Unknown	8
Time from diagnosis to transplantation, d	
<200	94
≥200	75
Unknown	6
Year of transplantation	
<2005	71
≥2005	104
HLA matching*	
0 mismatched loci	5
1 mismatched locus	36
2 mismatched loci	73
≥3 mismatched loci	42
Unknown	19
ABO matching	
Matched	56
Minor mismatched	49
Major mismatched	69
Unknown	1
Nucleated cells infused per 10^7/kg, median (range)	2.58 (.36-5.34)
CD34-positive cells infused per 10^5/kg, median (range)	.85 (.07-5.39)

* Number of mismatches was counted among HLA-A, -B (low-resolution typing), and DRB1 (high-resolution typing).

alone (n = 33), (2) cyclosporine + short-term methotrexate (MTX) (n = 45), and (3) cyclosporine + mycophenolate mofetil (MMF; n = 12). Tacrolimus-based prophylaxis was subdivided into 4 groups as follows: (1) tacrolimus alone (n = 37), (2) tacrolimus + short-term MTX (n = 32), (3) tacrolimus + MMF (n = 5), (4) and tacrolimus + prednisolone (n = 3). Ninety-four patients (54%) received CBT < 200 days after diagnosis. One hundred twenty-four (71%) patients underwent CBT with 2 HLA-mismatched loci. The numbers of infused nucleated and CD34-positive cells were 2.58×10^7/kg (range, .36 to 5.34×10^7/kg) and $.85 \times 10^5$/kg (range, .07 to 5.39×10^5/kg), respectively. Engraftment evaluation was possible in 125 patients (71%) within a median interval of 19 days after CBT (range, 7 to 46 days). Among the survivors, the median follow-up duration was 22.5 months (range, 0 to 74.5 months).

Prognostic Factors for Survival

The OS rates of 175 patients with ATLL who received CBT were 30.2% (95% confidence interval [CI], 23.0% to 37.4%) at 1 year and 20.6% (95% CI, 13.8% to 27.4%) at 2 years (Figure 1A). The cumulative incidence rates of ATLL-related mortality and TRM at 2 years were 31.9% (95% CI, 24.8% to 39.3%) and 46.4% (95% CI, 38.5% to 54.0%), respectively (Figure 1B). The following confounding factors affected survival: age, gender, disease status at transplantation, days from diagnosis to transplantation, date of transplantation, age at transplantation, conditioning regimen, number of infused nucleated and CD34-positive cells, ABO compatibility, HLA compatibility, GVHD prophylaxis, and the development of acute GVHD. A univariate analysis revealed that higher OS ($P < .05$) correlated with CR at transplantation, minor ABO incompatibility, the addition of other agents to calcineurin inhibitors (MTX or MMF), and the development of acute GVHD (Table 2). A multivariate analysis was performed to further examine the effects of an age <55 years, the development of acute GVHD as a time-dependent covariate coincident with CR at transplantation, minor ABO incompatibility, and the addition of other agents to calcineurin inhibitors (Table 3). Compared with the absence of GVHD, the development of acute GVHD was associated independently with higher OS (hazard ratio [HR], .10; 95% CI, .01 to 0.94; $P = .044$).

Effects of Acute GVHD on Survival

To further validate the effect of acute GVHD on OS, we examined survival according to the acute GVHD grade in a landmark analysis. The median time to onset of acute GVHD of any grade after transplantation was 21 days (range, 5 to 100 days). Acute GVHD occurred in 80 patients (46%) as

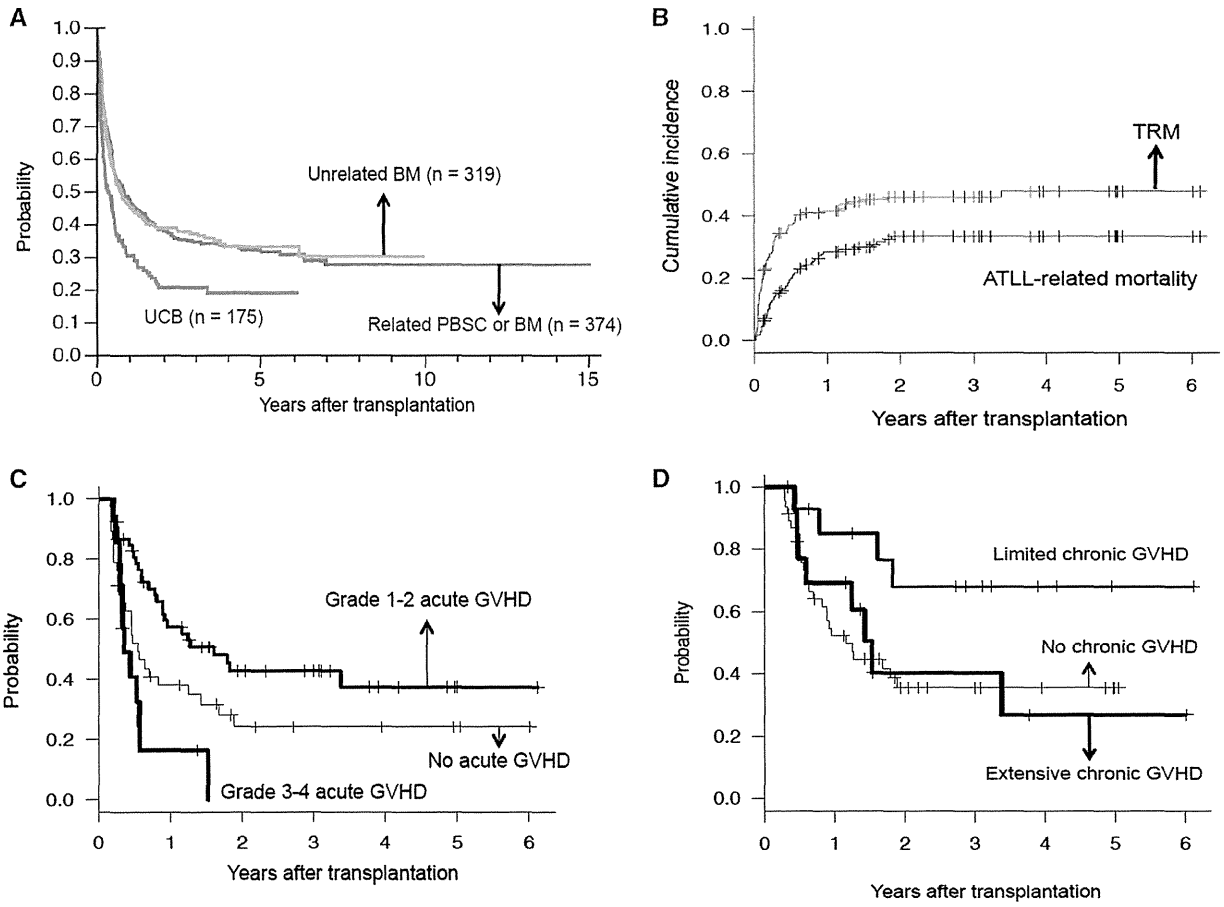

Figure 1. Survival, adult T cell leukemia/lymphoma (ATLL)-related mortality rates, and transplantation-related mortality (TRM) rates of patients receiving cord blood transplantation (CBT). (A) Kaplan-Meier curves of the estimated overall survival rates (OS) of ATLL patients treated with CBT. UCB, umbilical cord blood; PBSC, peripheral blood stem cells; BM, bone marrow, GVHD, graft-versus-host disease. (B) Cumulative incidence curves of ATLL-related mortality and TRM in patients treated with CBT. (C) Landmark plots of OS to determine the effects of acute GVHD. (D) Landmark plots of OS to determine the effects of chronic GVHD.

Table 2
Univariate Analysis of Risk Factors for Overall Survival

Variables		No.	OS		
			Two-Year OS (%)	95% CI	*P* Value
Age 1	<60 yr	134	23.0	15.0-31.0	.080
	≥60 yr	41	12.0	6.0-22.4	
Age 2	<55 yr	85	25.4	15.0-35.8	.100
	≥55 yr	90	15.6	7.0-24.2	
Sex	Female	70	22.3	11.5-33.1	.453
	Male	105	19.4	10.8-28.0	
Disease status at transplantation	CR	50	40.3	25.5-55.1	.003
	Not in CR	116	14.3	7.1-21.7	
Time from diagnosis to transplantation	<200 d	94	22.4	12.8-32.0	.752
	≥200 d	75	19.9	9.7-30.1	
Yr of transplantation	<2005	71	17.6	8.2-27.0	.160
	≥2005	104	23.1	13.5-31.5	
Conditioning regimen	FIC	63	20.2	9.8-30.6	.740
	RIC	108	20.2	11.8-28.6	
Infused nucleated cell dose ($\times 10^7$/kg)	<2	19	10.8	0-29.3	.290
	≥2	145	22.6	14.9-30.3	
Infused CD34 cell dose ($\times 10^5$/kg)	<1	97	23.3	13.9-32.7	.396
	≥1	66	19.1	8.0-30.2	
ABO matching	Matched	56	12.8	3.4-22.2	.024
	Minor mismatched	49	30.5	15.5-45.5	
	Major mismatched	69	20.5	9.9-31.1	
HLA matching	0 mismatched	5	30.0	0-77.4	.525
	1 mismatched	36	21.6	5.6-37.6	
	2 mismatched	73	24.6	14.3-35.9	
	≥3 mismatched	42	18.1	3.9-32.3	
GVHD prophylaxis 1	Cyclosporine-based	90	21.9	12.5-31.4	.710
	Tacrolimus-based	77	20.3	10.0-30.4	
GVHD prophylaxis 2 (cyclosporine/tacrolimus + other drug)	No	70	12.4	4.8-20.0	.003
	Yes	97	32.7	21.1-44.3	
Acute GVHD	No	59	16.8	5.7-27.9	<.0001
	Yes	80	29.4	18.2-40.6	

follows: grade 1, n = 23 patients; grade 2, n = 37 patients; grade 3, n = 14 patients; and grade 4, n = 6 patients. There was no significant difference in OS between patients with grades 1 and 2 GVHD ($P = 1.00$), in contrast to the difference between patients with grades 1 and 3 GVHD ($P = .013$). Moreover, based on the previous national survey analysis of the effect of acute GVHD on survival in patients with ATLL [5,15], the effect of acute GVHD on OS in the present study was evaluated using landmark plots (landmark day 60) according to the following 3 categories: (1) no acute GVHD (n = 38), (2) grade 1 to 2 acute GVHD (n = 53), and (3) grade 3 to 4 acute GVHD (n = 14). The 2-year OS rates for patients according to the acute GVHD grade were as follows: 24.2% (95% CI, 11.2% to 39.8%) without acute GVHD; 42.7% (95% CI, 28.1% to 56.6%) with grade 1 to 2 GVHD; and 0% with grade 3 to 4 GVHD (Figure 1C). These analyses demonstrated that the development of grade 1 to 2 acute GVHD was associated with higher OS compared with the absence of acute GVHD ($P = .048$), whereas the development of grade 3 to 4 acute GVHD was associated with lower OS compared with that in patients with grade 1 to 2 acute GVHD ($P = .0003$). The cumulative 2-year ATLL-related mortality rates according to the GVHD grades were as follows: 32.6% (95% CI, 19.7% to 46.1%) for grade 1 to 2 acute GVHD; 29.8% (95% CI, 8.2% to 55.6%) for grade 3 to 4 acute GVHD; and 45.9% (95% CI, 29.0% to 61.3%) for no acute GVHD. There was a trend toward a lower risk of relapse or progression in those who developed grade 1 to 2 acute GVHD relative to those without GVHD. Among patients with non-CR at transplantation, there was also a trend toward higher 2-year OS (36.7%; 95% CI, 18.7% to 54.9%) in those who developed grade 1 to 2 acute GVHD than in those without GVHD (15.6%; 95% CI, 3.4% to 35.9%). These data suggested a graft-versus-ATLL effect induced by CBT.

Table 3
Multivariate Analysis of Risk Factors for OS

Variables	OS		
	HR	95% CI	*P* Value
Age, yr			
<55	1		
≥55	1.15	.63-2.09	.652
Disease status at transplantation			
CR	1		
Not in CR	1.38	.73-2.63	.190
ABO matching			
Matched	1		
Minor mismatched	.56	.25-1.24	.152
Major mismatched	.77	.39-1.48	.337
GVHD prophylaxis (cyclosporine/ tacrolimus + other drug)			
No	1		
Yes	.76	.42-1.38	.365
Acute GVHD (time-dependent covariate)			
No	1		
Yes	.10	.01-.94	.044

Effects of Chronic GVHD on Survival

Chronic GVHD was evaluated in 74 patients who survived for at least 100 days after transplantation. Chronic GVHD occurred in 28 patients (37%) with a median time to onset of 115 days (range, 73 to 1287 days) after CBT. The effect of chronic GVHD on OS was evaluated using landmark plots (landmark day 100), and the 2-year OS results were as follows: no chronic GVHD (n = 46), 35.6% (95% CI, 21.0% to 50.0%); limited chronic GVHD (n = 15), 68.1% (95% CI, 35.4%

to 86.8%); and extensive chronic GVHD (n = 13), 40.4% (95% CI, 13.4% to 66.4%) (Figure 1D). There was a trend toward a higher OS among patients with limited chronic GVHD, but there were no significant differences relative to patients without chronic GVHD ($P = .10$) and those with extensive chronic GVHD ($P = .12$).

Cause of Death

At the last follow-up, 46 patients remained alive and 129 were deceased. The median follow-up time among the survivors was 22.5 months (range, 0 to 74.5 months). Disease progression (n = 52) was the leading cause of death. Infection was the cause of death in 40 patients (31%; bacterial, n = 27 patients; fungal, n = 3; viral, n = 8; and others, n = 2). Viral infection-related deaths were caused by the following pathogens: cytomegalovirus, n = 3; adenovirus, n = 2; human herpesvirus-6, n = 2; and varicella-zoster virus, n = 1. Among the 27 patients who succumbed to bacterial infection, 16 died before engraftment at a median of 17 days after CBT (range, 7 to 38 days). Among the 20 patients who developed severe acute grade 3 to 4 GVHD, 2 remain alive without disease progression. However, 9 of the 20 patients died of GVHD, 5 of disease progression, and 4 of infection.

The Fine and Gray proportional hazards model was applied to identify the variables affecting ATLL-related mortality and TRM. The pretransplantation variables included age, gender, disease status at CBT, days from diagnosis to transplantation, age at transplantation, conditioning regimen, number of infused nucleated cells, ABO compatibility, HLA compatibility, and GVHD prophylaxis. The following pretransplantation factors associated with a higher risk of ATLL-related mortality were identified in a multivariate analysis: not in CR at CBT (HR, 3.37; 95% CI, 1.12 to 10.2; $P = .032$) and an age > 55 years at CBT (HR, 2.32; 95% CI, .98 to 5.48; $P = .054$). The following pretransplantation factors were associated with a marginally higher risk of TRM: lower number of infused nucleated cells ($\geq 2 \times 10^7$/kg versus $< 2 \times 10^7$/kg; HR, .56; 95% CI, .30 to 1.02; $P = .059$) and GVHD prophylaxis with a calcineurin inhibitor alone (additional agents plus calcineurin inhibitors versus calcineurin inhibitors alone; HR, .60; 95% CI, .34 to 1.07; $P = .064$).

DISCUSSION

We present here the results of the largest retrospective study of ATLL patients receiving CBT; these results have extended our knowledge relative to that gained from other studies, which were limited by the numbers of cases [15,20,21]. Because graft source selection is strongly influenced by the donor availability, it is difficult to directly compare the outcomes of CBT with those of other allo-HSCT modalities. Nevertheless, the outcome of CBT for ATLL in the previous nationwide survey, with a 3-year OS rate of 17%, was clearly unsatisfactory because the study period corresponded with the developmental phase of CBT in adult patients [15]. Recent improvements in the outcome of CBT have been expected after optimization of the number of cells used for CBT and the improved HLA-compatibility of cord blood units [29-31]. Consequently, a recent nationwide survey data of adults with acute non-ATLL leukemia revealed no differences in the outcome of CBT in comparison with those of other allo-HSCT modalities [18,19]. However, the updated data (through December 2009) indicated that CBT for ATLL remained associated with a poorer 3-year OS of 20.6%, compared with OS of 34.4% among the 374 patients who received related BM or PBSC and 37.1% among the 319 patients who received unrelated BM ($P < .0001$) (Figure 1A). Therefore, the aim of the present study focused on the feasibility of CBT in the context of a larger cohort of patients with ATLL.

In the present study, 2 important findings were identified regarding CBT for ATLL. First, CBT cured patients with ATLL partly through a graft-versus-ATLL effect. Second, the high rate of TRM (approximately 50%) remains a significant problem. The OS curve for ATLL patients who received CBT reached a plateau by 3 years, suggesting long-term survival of selected patients, although the outcome of CBT for ATLL (3-year OS, 20%) did not compare favorably with those of other allo-HSCT modalities. Regarding the prognostic factors affecting survival, our present univariate analysis identified the 5 following significant variables associated with higher OS: (1) age, (2) disease status at transplantation, (3) ABO compatibility, (4) addition of agents such as MTX or MMF to calcineurin inhibitors for GVHD prophylaxis, and (5) development of acute GVHD. Further, the multivariate analysis revealed that the development of acute GVHD was independently associated with better OS relative to the absence of acute GVHD. A landmark analysis showed that the development of grade 1 to 2, or so called mild-to-moderate acute GVHD, was associated with better OS when compared with the absence of acute GVHD. There was also a trend toward a lower risk of relapse or progression with the development of acute GVHD when compared with the absence of GVHD and better OS in patients with limited chronic GVHD. Taken together, these data suggest the presence of a curative graft-versus-ATLL effect conferred by CBT.

However, it is typically difficult for physicians to optimize the effects of acute GVHD to prevent disease progression via graft-versus-ATLL. Therefore, a more realistic attempt would be the control of pretransplantation factors that might affect the CBT outcome and, thus, enhance the benefit of allo-HSCT. The multivariate analysis performed herein with respect to ATLL-related deaths identified disease status at CBT as the most important factor. ATLL usually resists conventional chemotherapy and must be treated soon after diagnosis because of the rapid proliferation of tumor cells, which generates a high tumor burden [2,3]. In the future, novel agents, such as mogamulizumab, a humanized anti-CCR4 monoclonal antibody, might improve CBT-associated survival by decreasing the tumor burden before transplantation [32-35]. Another possibility for improving survival might be reducing the time from diagnosis to transplantation while patients with ATLL remain chemosensitive. Moreover, CBT provides a considerable advantage for patients who require urgent allo-HSCT to combat aggressive ATLL.

In the present study, we have shown that CBT is feasible and curative. However, the high rate of TRM remained a significant problem. Bacterial infection caused the highest incidence of death (21%) during the neutropenic period. The infusion of lower numbers of nucleated cells ($< 2 \times 10^7$/kg), which is usually associated with delayed engraftment, was marginally associated with TRM. Neutrophil recovery is slower in patients treated via CBT, and immunosuppressed patients with ATLL might be at an increased risk of developing more frequent opportunistic infections [36]. Improved supportive care to prevent bacterial infection is required after CBT for patients experiencing a prolonged neutropenic period. The ongoing development of better graft engineering [37] or double-CBT [38] might facilitate rapid neutrophil recovery and, thus, help to reduce the TRM rate in CB recipients.

The present study has several limitations. First, our results concerning the effect of chronic GVHD on survival should be interpreted with caution because the relatively small number of patients who developed chronic GVHD did not allow us to evaluate the effect of this condition on survival in a multivariate analysis. Instead, we were limited to performing a landmark analysis of OS according to the severity of chronic GVHD. Certainly, we detected a trend toward higher OS in patients with limited chronic GVHD when compared with patients without chronic GVHD, suggesting the possible presence of a graft-versus-ATLL effect. However, these results might be biased because of insufficient statistical power. Our future studies will assess the effect of chronic GVHD on the outcome of CBT for the treatment of ATLL after a long-term follow-up. Although the present study employed, to our knowledge, the largest cohort of CBT-treated patients to date and our results demonstrated that CBT is a feasible and effective treatment, this was a retrospective analysis. Therefore, this finding requires confirmation in prospective studies. To establish reliable criteria for CBT administration, a prospective multicenter clinical trial is underway in Japan to evaluate the safety and efficacy of CBT combined with Flu, Mel, and low-dose TBI (4 Gy) along with GVHD prophylaxis (tacrolimus and MMF [39]).

In conclusion, CBT is feasible and effective for patients with ATLL and acts via a graft-versus-ATLL effect. However, the outcome of CBT is unsatisfactory when compared with those of other allo-HSCT modalities. The high rate of TRM must be reduced, and the development of novel strategies is required to further improve the outcome of CBT.

ACKNOWLEDGMENTS

The authors thank the physicians and data managers at the institutes who contributed valuable data regarding ATLL-related transplantation to the Japan Society for Hematopoietic Cell Transplantation. We also thank all members of the data management committees of the JSHCT. This work was supported in part by MEXT KAKENHI Grant Number 25461453 (K.K.) and H22-Ganrinsho-Ippan-028 (N.U.).

Conflict of interest disclosure: The authors declare no competing financial interests.

Authorship contributions: K.K., I.C., A.W., and A.U. designed the study; K.K., I.C., A.W., N.U., S.T., Y. Moriuchi, Y. Miyazaki, H.N., E.O., M.M., T.E., K.A., H.S., K. Kato, R.S., T.Y., and A.U. collected and analyzed the data; K.K. and T.Y. performed the statistical analysis. K.K. wrote the manuscript and created the figures and tables; all authors critically reviewed the manuscript and read and approved the final version of the manuscript.

Financial disclosure: The authors have nothing to disclose.

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Eur Radiol
DOI 10.1007/s00330-014-3565-3

CHEST

Chest HRCT findings in acute transformation of adult T-cell lymphoma/leukemia

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Received: 16 July 2014 / Revised: 24 October 2014 / Accepted: 11 December 2014

Abstract
Objectives To assess chest high-resolution computed tomography (HRCT) findings in patients with acute transformation of adult T cell leukaemia/lymphoma (ATLL).
Methods We retrospectively identified 72 consecutive patients at our institution with ATLL between October 2000 and March 2014. The cases included acute type (n=20), lymphoma type (n=21), smouldering type (n=24) and chronic type (n=7). Sixteen (7 men, 9 women; aged 36–85 years, mean 63.3 years) of 31 patients (24 with smouldering and seven with chronic type; 51.6 %) developed acute transformation of ATLL, and had undergone chest HRCT examinations. Parenchymal abnormalities, enlarged lymph nodes, pericardial effusion, pleural effusion and skin lesions were evaluated on HRCT.
Results Chest HRCT of 15 of the 16 patients showed abnormal findings, including ground-glass opacity (GGO) (n=8), consolidation (n=5), interlobular septal thickening (n=5) and nodules (n=5). Pleural effusion was found in five patients, lymph node enlargement in 10 patients and multiple skin thickening in two patients.
Conclusions Almost all patients with acute transformation of ATLL had abnormal findings on chest HRCT, which consisted mainly of lymph node enlargement, GGO, interlobular septal thickening, nodules and bilateral pleural effusions.

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Key points
- *The recognition of CT findings of acute transformation is important*
- *Almost all patients with acute transformation have abnormal findings on HRCT*
- *Characteristic CT features are present in acute transformation of indolent ATLL*

Keywords Computed tomography · Chest · Adult T cell leukemia/lymphoma · Acute transformation · HTLV-1

Abbreviations

ATLL	Adult T cell leukaemia/lymphoma
BAL	Bronchoalveolar lavage
GGO	Ground-glass opacity
HRCT	High-resolution computed tomography
HTLV-1	Human T-lymphotropic virus type 1
LDH	Lactate dehydrogenase
TBLB	Transbronchial lung biopsy

Introduction

Human T-lymphotropic virus type 1 (HTLV-1), which is prevalent in southwestern Japan and the Caribbean basin [1], is aetiologically associated with adult T cell leukaemia/lymphoma (ATLL). The diversity in clinical features and prognosis of patients with ATLL has led to its categorization into four subtypes: acute, lymphoma, chronic and smouldering. These are defined by organ involvement, lactate dehydrogenase (LDH) and calcium values. In patients with acute type and lymphoma type (aggressive ATLL), intensive chemotherapy is usually recommended. Patients with aggressive ATLL

Published online: 11 January 2015

have a very poor prognosis owing to intrinsic chemoresistance and frequent infectious complications because of immune deficiency. Patients with chronic type and smouldering type (indolent ATLL), however, have a better prognosis than those with aggressive ATLL, and watchful waiting until disease progression has been recommended. However, the long-term prognosis of patients with indolent ATLL is not good without a plateau phase in the survival curve [2]. There are several reports documenting acute transformation to aggressive type in up to 40 % of patients with indolent ATLL [2].

Okada et al. reported thoracic computed tomography (CT) findings based on radiological features in 87 patients with ATLL [3]. These CT findings mainly consisted of ground-glass opacity (GGO), centrilobular nodules, and thickening of the bronchovascular bundles in the periphery. Recently, Hanaka et al. reported a case of ATLL with rapid progression of pulmonary areas of GGO and multiple nodules, resulting from acute transformation of chronic ATLL [4]. To our knowledge, no other English-language studies on CT features in patients with acute transformation of ATLL have been published. The purpose of this study was to assess chest high-resolution CT (HRCT) findings in patients with acute transformation of ATLL that may be of clinical significance.

Materials and methods

Patients

Our institutional review board approved this retrospective study and waived the requirement for informed consent.

On the basis of the patient population at our institution, we retrospectively identified 72 consecutive patients with ATLL between October 2000 and March 2014. The patients consisted of 20 with acute type, 21 with lymphoma type, 24 with smouldering type and seven with chronic type. Of the 31 patients with smouldering type or chronic type, 16 (seven men, nine women; aged 36–85 years, mean 63.3 years; 51.6 %) developed acute transformations by serological and clinical findings, and had undergone chest HRCT. At the same time, there were no patients diagnosed with infectious disease by serological tests and clinical findings.

ATLL was diagnosed by positive HTLV-1 antibody and the presence of abnormal lymphocytes with convoluted nuclei (ATLL cells) in the peripheral blood or histological findings compatible with a diagnosis of ATLL in biopsied tissue.

The diagnosis for acute transformation of ATLL was established by fulfilling the diagnostic criteria for acute type or lymphoma type of ATLL. The periods between the diagnosis of smouldering type or chronic type and acute exacerbation of ATLL were 1– 124 months (mean 25.8 months). The patients presented with several symptoms, such as general fatigue in eight, fever in seven, eruption in seven, lymph node enlargement in six, chest pain in one and joint pain in one.

CT examinations

HRCT examinations were performed with a variety of scanners, volumetrically with a multi-detector CT with 1-mm reconstruction from the apex of the lung to the diaphragm. The images were obtained with the patient in the supine position at full inspiration. Images were captured at window settings that allowed viewing of the lung parenchyma (window level −600 HU; window width 1,500 HU) and the mediastinum (window level 10–30 HU; window width 300 HU).

A pulmonary CT was performed within 1 day to 1 month (mean 18.5 days) after the onset of fever, general fatigue, lymph node enlargement and other abnormal conditions. Intravenously administered contrast material was used in six patients.

CT image interpretation

Two chest radiologists (with 27 and 12 years of experience in interpretation of chest CT images), who were aware of the underlying diagnoses, retrospectively and independently interpreted the CTs. Conclusions were reached by consensus.

CT images were evaluated for the presence and extent of abnormalities, including GGO, consolidation, bronchial wall thickening, centrilobular nodules, intralobular reticular opacity, nodules, cavity, interlobular septal thickening and lymph node enlargement. The presence or absence of pleural effusion and pericardial effusion was also recorded. In addition, the combination of abnormalities was assessed. Radiological features were defined according to the glossary of terms established by the Fleischner Society [5].

The distribution of parenchymal disease was also noted. We assessed whether abnormal findings were located unilaterally or bilaterally. If the main lesion was predominantly located in the inner third of the lung, the disease was classified as centrally distributed. If the main lesion was predominantly located in the outer third of the lung, the disease was classified as peripherally distributed. If the lesions showed no predominant distribution, the disease was classified as randomly distributed. Additionally, zonal predominance was classified as upper, lower or random. Upper-lung zone predominance indicated that most abnormalities were observed at a level above the tracheal carina, while lower-zone predominance indicated that most abnormalities were located below the upper zone. When abnormalities showed no clear zonal predominance, the lung disease was classified as randomly distributed.

Follow-up examinations after treatment were also assessed.

Results

CT patterns

Chest CTs showed abnormalities in 15 of the 16 patients (93.8 %) with acute transformation of ATLL (Table 1). In nine of the 15 patients (60.0 %), parenchymal abnormal findings were found, in which GGO (n=8; 53.3 %; Figs. 1 and 2) was the most frequently observed abnormality, followed by consolidation (n=5; 33.3 %; Figs. 1 and 2), interlobular septal thickening (n=5; 33.3 %; Figs. 1, 2, and 3) and nodules (n=5; 33.3 %; Fig. 1). Intralobular reticular opacity (n=3; 20.0 %) and cavity (n=1; 6.7 %) were also observed. Centrilobular nodules could not be found.

Pleural effusions were identified in five of the 15 patients (33.3 %); four were bilateral pleural effusions (26.7 %) and one was unilateral pleural effusion (6.7 %). In one of the five patients (20.0 %), parenchymal abnormalities were not observed.

Mediastinal and/or axillary lymph node enlargements were observed in 10 patients (66.7 %): mediastinum lymph node enlargement alone in one (6.7 %); axillary lymph node enlargement alone in three (20.0 %; Fig. 4) and both in six (40.0 %). Enlarged lymph nodes were found in the paratracheal, tracheobronchial and subcarinal regions. Hilar lymph node enlargement was not seen in the patients.

Thickening of the skin was found in two patients (13.3 %; Fig. 5), in multiple regions such as the anterior and posterior chest wall. In these two patients, there were no abnormal findings in the lung parenchyma.

Table 1 CT findings in 15 patients

Findings	No. of patients
Ground-glass opacity	8 (53.3)
Consolidation	5 (33.3)
Interlobular septal thickening	5 (33.3)
Nodule/mass	5 (33.3)
Intralobular reticular opacity	3 (20.0)
Bronchial wall thickening	2 (13.3)
Cavity	1 (6.7)
Centrilobular nodules	0 (0)
Pericardial effusion	0 (0)
Pleural effusion	5 (33.3)
Unilateral	1 (6.7)
Bilateral	4 (26.7)
Lymph node enlargement	10 (66.7)
Mediastinum	7 (46.7)
Axillary	9 (60.0)
Skin lesions	2 (13.3)

Data in parentheses are percentages

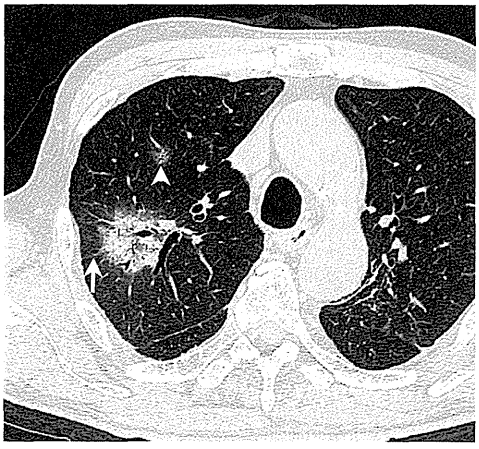

Fig. 1 Acute transformation (acute type) in a 67-year-old male patient with smouldering type ATLL, 21 days after the onset of fever. Transverse CT image (1-mm thickness) at the level of the aortic arch shows mass-like consolidation with surrounding GGO and air bronchogram and interlobular septal thickening (*arrow*). Small nodule is present in the right upper lobe (*arrowhead*)

The most frequently observed combination of abnormalities was GGO and interlobular septal thickening (n=5; 33.3 %; Figs. 1 and 2), followed by GGO and lymph node enlargement (n=5; 33.3 %), GGO and consolidation (n=4; 26.7 %; Figs. 1 and 2), GGO and nodules (n=4; 26.7 %; Fig. 1), GGO and pleural effusion (n=4; 26.7 %) and pleural effusion and lymph node enlargement (n=4; 26.7 %).

Disease distribution

Among the nine patients with parenchymal abnormalities, abnormal findings were found bilaterally in all of the patients,

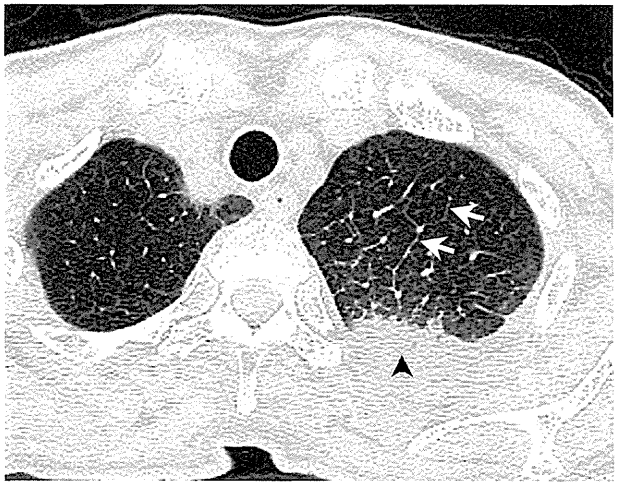

Fig. 2 Acute transformation (acute type) in a 77-year-old female patient with smouldering type ATLL, 7 days after the onset of fever and general fatigue. Transverse CT image (1-mm thickness) at the level of the left upper lobe shows consolidation (*arrowhead*), GGO and interlobular septal thickening (*arrows*)

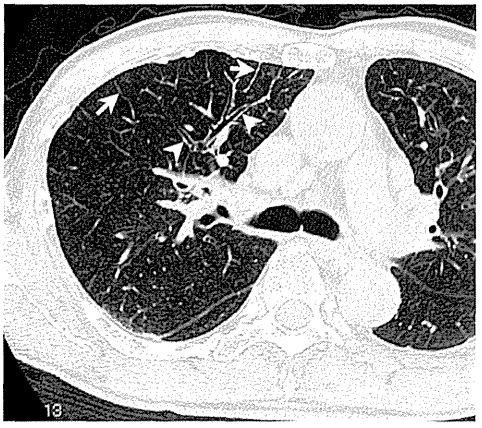

Fig. 3 Acute transformation (acute type) in a 69-year-old male patient with smouldering type ATLL, 10 days after the onset of fever. Transverse CT image (1-mm thickness) at the level of the tracheal carina shows interlobular septal thickening (*arrows*) and bronchial wall thickening (*arrowheads*)

and were randomly distributed in eight of the patients (88.9 %). The remaining patient showed a peripheral distribution (11.1 %).

The predominant zonal distribution was the upper zone in two patients (22.2 %), the lower zone in one patient (11.1 %) and a random distribution in six patients (66.7 %).

Follow-up study

All 15 patients underwent chemotherapy. In 11 patients, abnormal findings improved on follow-up CT examinations or chest radiographs, whereas in the remaining four patients abnormal findings worsened and the patients died.

There were no significant differences in the initial HRCT patterns and distribution of disease between the improved patients and the deceased patients.

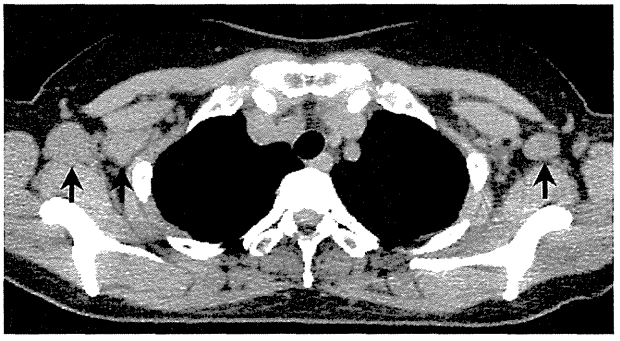

Fig. 4 Acute transformation (acute type) in a 43-year-old female patient with chronic type ATLL, 14 days after the onset of general fatigue and lymph node enlargement of the neck and axillary regions. Transverse CT image (1-mm thickness) at the level of the axillary regions shows multiple axillary lymph node enlargement (*arrows*)

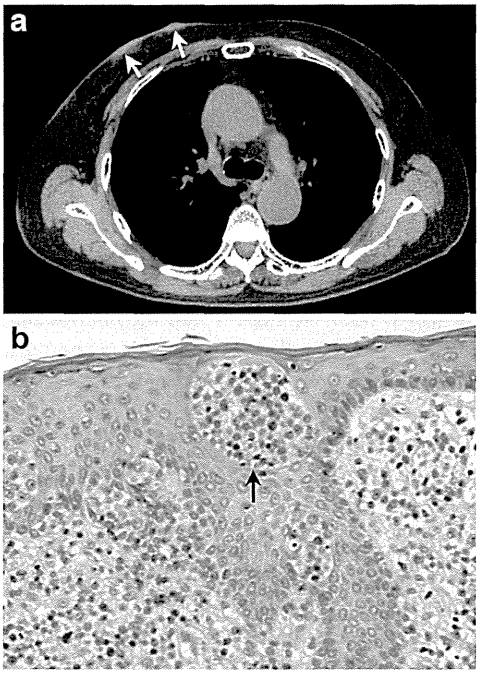

Fig. 5 Acute transformation (lymphoma type) in a 73-year-old female patient with smouldering type ATLL, 20 days after the onset of eruptions and lymph node enlargement of the inguinal regions. **a** Transverse CT image (1-mm thickness) at the level of the tracheal carina shows multiple thickening of the skin (*arrows*). **b** Photomicrograph of the biopsy specimen obtained from the thickened skin of the right chest wall shows a microabscess (*arrow*) and dens dermal infiltration by lymphoid cells with nuclear atypia

Pathological findings

Skin biopsies were performed in two patients with thickening of the skin. The pathological findings showed a microabscess and dens dermal infiltration by lymphoid cells with nuclear atypia.

Transbronchial lung biopsy (TBLB), surgical lung biopsy or bronchoalveolar lavage was not performed because patients were in poor general health and needed to undergo immediate chemotherapy. Additionally, postmortem studies in four deceased patients were not undertaken.

Discussion

ATLL was first described in 1977 as a distinct clinicopathological entity with a suspected viral aetiology [6]. Subsequently, HTLV-1 was isolated as a carcinogenic pathogen. HTLV-1 infects approximately 15–20 million people worldwide, with endemic areas in southwestern Japan, the Caribbean and Africa. After prolonged latency periods (10–30 years), approximately 0.5–5.0 % of HTLV-1-infected individuals will develop ATLL [7–9]. The three major routes of HTLV-1

transmission are mother-to-child via breast-feeding, sexual intercourse and blood transfusions. HTLV-1 infection early in life, in the form of breast-feeding, is crucial in the development of ATLL. ATLL is defined as a neoplastic clonal growth of HTLV-1-infected cells. ATLL can present in various clinical manifestations by involving many organs, including lungs, skin, gastrointestinal tract, the central nervous systems and bones. The diverse clinical features of this disease have led to its subclassification as acute, lymphoma, chronic and smouldering subtypes [10]. The first is the smouldering type, in which more than 5 % of T lymphocytes are abnormal, the peripheral blood contains less than 4,000 lymphocytes per microlitre, there is no hypercalcaemia, LDH level is up to 1.5-fold the normal upper limit, there is no lymphadenopathy and no involvement of extranodal organs except the skin or lungs. This type is the least common, accounting for approximately 5 % of ATLL. The second is the chronic type, in which lymphocytosis occurs (defined as T lymphocytosis greater than 4,000/μL), LDH is less than twice the normal upper limit, no hypercalcaemia is present and there is possible lymph node, liver, spleen, skin and lung involvement. This type accounts for approximately 15–20 % of ATLL. The third is the lymphoma type, in which histologically proven lymph node enlargement is present but there is no lymphocytosis (defined as less than 1 % abnormal T lymphocytes). This type accounts for approximately 20 % of ATLL. Patients frequently have an elevated LDH level and can have hypercalcaemia. The fourth is the acute type, for patients not classified into any of the above three types, and occurs in approximately 55–60 % of ATLL. Patients with the acute type present with systemic symptoms, organomegaly, lymphadenopathy and an elevated LDH level. The white blood cell count is usually greater than 20,000/mL.

The median survival time is 6.2 months for the acute type, 10.2 months for the lymphoma type and 24.3 months for the chronic type; 62.8 % of patients with the smouldering type were still alive after 4 years [10].

Because ATLL patients present with a variety of clinical symptoms and course, it is important for the clinician to differentiate between aggressive ATLL (acute type and lymphoma type), necessitating immediate treatment, and indolent ATLL (chronic type and smouldering type) that does not require specific treatment. In the last two types, the disease has an indolent initial course but frequently progresses to acute type ATLL. Ishitsuka et al. reported that, in 26 patients with smouldering type ATLL, 10 patients (38.5 %) developed acute transformation to acute or lymphoma type ATLL, and died despite chemotherapy [11]. Takasaki et al. evaluated the long-term prognosis of 60 Japanese patients with indolent ATLL [2]. Among the patients, 44 (73.3 %) progressed to aggressive ATLL (all were acute type), and 41 (68.3 %) died. The median time to acute transformation was 18.8 months (range 0.3 months to 17.6 years).

In our study, 16 of 31 patients (24 with smouldering and seven with chronic type; 51.6 %) developed acute transformation of ATLL (14 patients with acute type, two with lymphoma type) and four of these patients (25 %) died. The mean time between the diagnosis of smouldering or chronic type and acute exacerbation of ATLL was 25.8 months (range 1–124 months).

There have been several reports of the mechanisms of acute transformation of ATLL. Tsukasaki and colleagues compared the gene-expression profiles of four pairs of chronic and acute ATLL samples using oligonucleotide microarrays to elucidate the differences in gene expression during progression to acute ATLL [12]. They identified 203 genes that were commonly up-regulated in acute- vs. chronic-phase samples, and an additional 91 commonly down-regulated genes. Some of the up-regulated genes were located in amplified regions identified by comparative genomic hybridization in the corresponding chronic/acute ATLL samples. Tsukasaki et al. concluded that distinct sets of genes that are known to be critical in cellular transformation and/or activation are up- or down-regulated during the transition to the acute phase of ATLL.

A close relationship between strongyloidiasis and HTLV-1 has also been reported [13–18]. Nakada et al. studied the prevalence of HTLV-1 antibody in sera from *Strongyloides* carriers and controls [13]. In their study, 99 of 166 *Strongyloides* carriers (59.6 %) had HTLV-1 antibodies but 595 of 2,962 controls (20.1 %) had HTLV-1 antibody. Conversely, the detection rate of faecal larvae among the *Strongyloides*-seropositive patients was significantly higher in patients with the HTLV-1 antibody than in those without the HTLV-1 antibody. These findings suggest an effect of a concurrent HTLV-1 infection on the course and intensity of *Strongyloides* infection [14].

Nakada et al. reported that 36 patients with strongyloidiasis were seropositive for HTLV-1, and that 14 of these patients (38.9 %) had monoclonal integration of HTLV-1 proviral DNA in their blood lymphocytes [15]. They concluded that, although the immunodeficiency caused by HTLV-1 could predispose patients to hyperinfestation by *Strongyloides*, parasitic and retroviral infestations might be important co-factors leading to the development of ATLL. Nonetheless, the mechanisms of acute exacerbation of ATLL remain unclear. In the present study, *Strongyloides stercoralis* infection in patients with acute transformation of ATLL was not examined.

With regard to the radiological findings in ATLL, Okada et al. reported thoracic CT findings in 87 patients with ATLL, of which 60 patients (69.0 %) had abnormal findings [3]. They consisted mainly of GGO (62 %), centrilobular nodules (42 %), bronchovascular bundles thickening (37 %), interlobular septal thickening (28 %) and nodules (22 %). Moreover, pleural effusion and lymph node enlargement were found frequently in 37 % and 45 %, respectively. In 46 patients, CT–pathology correlation was performed using surgical or

autopsy specimens. Pathologically, these CT findings corresponded to atypical lymphocyte infiltration along the interstitium and the alveolar spaces. As for CT findings in acute transformation of ATLL, there is only one case report [4]. Hanaka et al. reported a case of a 48-year-old Japanese man with acute transformation from ATLL chronic type [4] in which CT findings were correlated with pathological findings using TBLB specimens. The chest CT images showed GGO and nodules in both lungs. Pathologically, the extent of GGO corresponded to the partial infiltration of ATLL cells and foam cells into the alveolar walls, and the nodules corresponded to thickening of the alveolar walls, mild alteration of alveolar structures and overt precipitation of fibrin.

Distinguishing between acute transformation of ATLL and infection in patients with indolent ATLL is important because the treatment strategies are quite different. In the clinic, the diagnosis of pneumonia is established by the isolation of causative pathogens from sputum, bronchoalveolar lavage, urine or blood, along with respiratory symptoms and abnormal findings on chest radiographs. Additionally, the elevation of the serum level of β-D-glucan or antigen for each type of fungus antigen in combination with HRCT findings is suggestive of fungal infection and *Pneumocystis jirovecii* pneumonia.

Increased numbers of ATLL cells, elevated LDH level, hypercalcaemia and lymphadenopathy were findings suggestive of acute transformation in patients with indolent ATLL. Bronchoalveolar lavage fluid or transbronchial lung biopsy specimens provide clues to the differential diagnosis of pulmonary manifestation of ATLL acute transformation versus infections; however, patients with ATLL often have poor general status and it is difficult to undergo a transbronchial lung examination. Moreover, immediate treatment should be started. This was the case in the present study.

Recently, Okada and colleagues reported HRCT findings in 749 pneumonia patients (385 with community-acquired pneumonia and 364 with nosocomial pneumonia: 86 *Streptococcus pneumoniae*, 211 *Haemophilus influenzae*, 109 *Moraxella catarrhalis*, 83 *Staphylococcus aureus*, 80 *Klebsiella pneumoniae*, 33 *Streptococcus milleri*, 35 *Pseudomonas aeruginosa*, 40 *Chlamydia pneumoniae*, 42 *Mycoplasma pneumoniae* and 30 seasonal influenza virus); this included 136 patients with malignancy [19–27]. In those reports, the CT findings of interlobular septal thickening, lymph node enlargement and nodules were found in 2.9–15.0 % (mean 9.5 %), 0–18.2 % (mean 4.3 %) and 0–18.2 % (mean 7.9 %), respectively. In the present report of patients with acute transformation of ATLL, these CT findings were found in 33.3 %, 66.7 % and 33.3 %, respectively. These frequencies were higher in patients with acute transformation of ATLL than in patients with pneumonia. Moreover, thickened skin and axillary lymph node enlargement could not be found in patients with each type of pneumonia. In patients with cytomegalovirus pneumonia and *Pneumocystis jirovecii* pneumonia, HRCT finding of nodules is often seen; however, in cytomegalovirus pneumonia, interlobular septal thickening, lymph node enlargement and thickening of the skin are rarely seen [28, 29]. In *Pneumocystis jirovecii* pneumonia, interlobular septal thickening or lymph node enlargement is relatively rarely seen [30].

Therefore, the HRCT of interlobular septal thickening, lymph node enlargement (especially in axillary regions) and thickened skin lesions, which may be non-specific findings, are suggestive of acute transformation in patients with indolent ATLL, along with clinical findings.

It should be noted that there are several limitations to the present study. First, this was a retrospective study and CT image interpretation was performed by consensus. Second, this study included only a small number of patients. Differences in HRCT findings between acute type and lymphoma type in acute transformation of ATLL could not be assessed. Third, the differences between acute transformation of ATLL and infection in indolent ATLL patients were not studied on HRCT. Therefore, it might be difficult to generalize the HRCT findings observed in this study as 'characteristic findings'. Fourth, no correlation with pathological findings of the lungs was possible because patients were in poor general health. Finally, the HRCT images were obtained using different protocols.

In summary, almost all of the patients with acute transformation of ATLL had abnormal findings on chest HRCT, which mainly consisted of lymph node enlargement, GGO, interlobular septal thickening, nodules and bilateral pleural effusion. In particular, lymph node enlargement in axillary regions, interlobular septal thickening and thickened skin lesions are suggestive of acute transformation in patients with indolent ATLL, along with clinical findings.

Acknowledgments The scientific guarantor of this publication is Fumito Okada. The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article. The authors state that this work has not received any funding. No complex statistical methods were necessary for this paper. Institutional review board approval was not required because this study was retrospective. Written informed consent was not required for this study because this study was retrospective. None of the study subjects or cohorts have been previously reported. Methodology: retrospective, diagnostic or prognostic study, performed at one institution.

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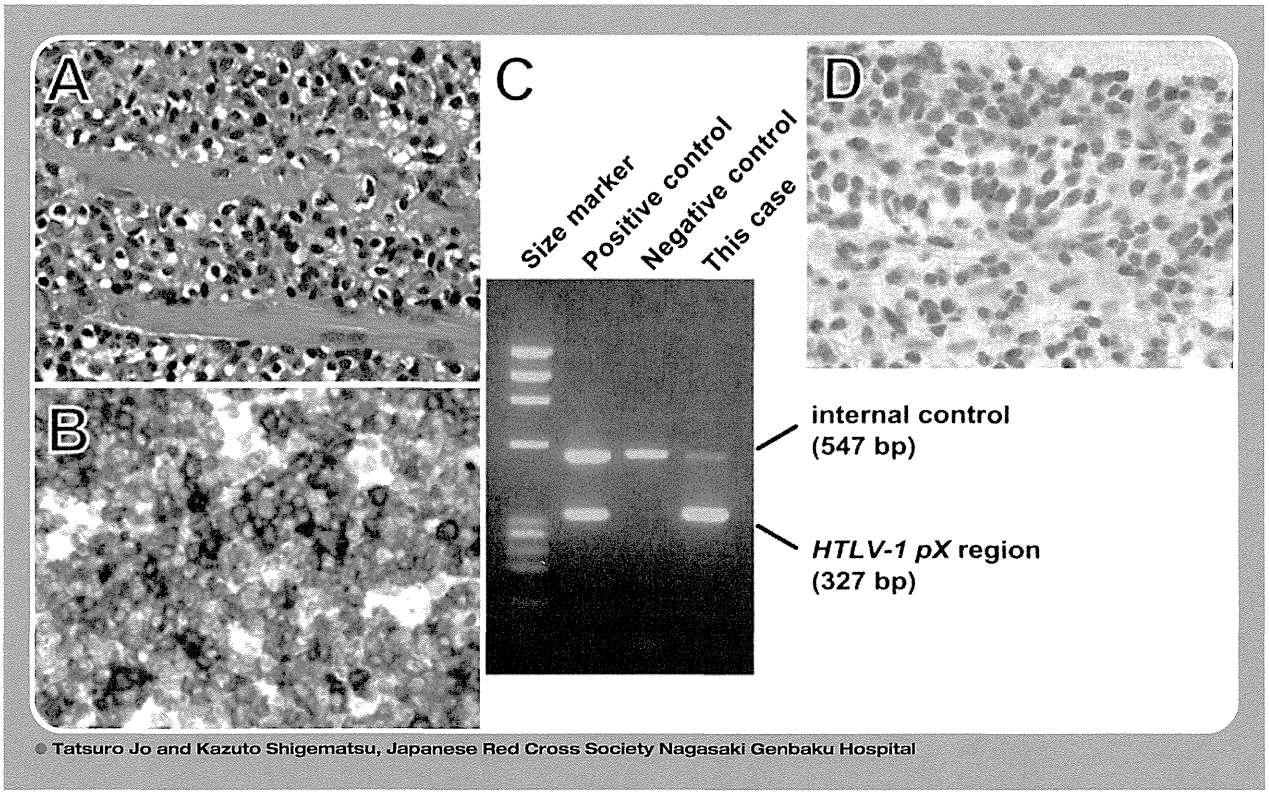
bloodwork
IMAGES IN HEMATOLOGY

Extensive and destructive invasion of adult T-cell leukemia/lymphoma cells into systemic muscular tissues



A 64-year-old woman was admitted to the hospital because of systemic body edema and a gait disturbance caused by muscle weakness. At the time of her admission, a complete blood count panel showed a white blood cell level of 10.1 × 10^9/L (85% neutrophils, 6% lymphocytes, 1.5% monocytes, 7.5% eosinophils) without abnormal lymphocytes, and anemia and thrombocytopenia were absent. Although the lactate dehydrogenase level was normal, the creatine phosphokinase level was elevated to 2546 U/L. A computed tomography scan revealed systemic edema, without lymph node swelling or hepatosplenomegaly. A high short-time inversion recovery signal was observed in almost all muscles on magnetic resonance imaging. In addition, antihuman T-lymphotropic virus type I (HTLV-I) antibody was positive, and soluble interleukin 2 receptor was elevated to 28 300 U/mL. A muscle biopsy of the left biceps brachii showed abnormal lymphocytes invading and destroying the muscle tissue (panel A, hematoxylin and eosin [×400]). Most of these lymphocytes were CD4 and CCR4 positive (panel B, CCR4 staining [×400]), and integrated with the HTLV-I genome (panel C, PCR analysis for HTLV-1 pX region: 1, size marker; 2, positive control; 3, negative control; 4, this patient), and Tax positive (panel D, p40Tax staining [×400]).

This is a rare case of extensive and destructive invasion of adult T-cell leukemia/lymphoma (ATLL) cells into systemic muscular tissues, without the proliferation of ATLL cells in the peripheral blood and lymph nodes.