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Original Article

A case series of adult T-cell leukemia-lymphoma, associated with human T-cell leukemia virus type-1, at a single center in a non-viral-endemic metropolitan area

Yu Akuzawa, Kunihiro Tsukasaki, Tsuyoshi Saeki, Daisuke Okamura, Maho Ishikawa, Tomoya Maeda, Mika Kohri, Naoki Takahashi, Akira Matsuda, Nobutaka Kawai, Norio Asou

We examined 13 patients with adult T-cell leukemia-lymphoma (ATL) diagnosed between 2007 and 2018 at a single center in a metropolitan area non-endemic for human T-cell leukemia virus type I (HTLV-1). The median age of the patients (eight male, five female) was 65 years (range, 48-83). The time from onset of symptoms to referral to our center was relatively short (median, 2 months; range, 1-9 months). Upon referral, all patients were suspected to have lymphoma, five were examined for soluble IL-2 receptor and two were examined for anti-HTLV-1 antibody. In ten of the 13 (77%), the patient themselves or their relatives were born in Kyushu. The birth places of the remaining three patients were unknown. Three patients (23%) had family histories of lymphoma. They all exhibited aggressive ATL (five acute, eight lymphoma type); however, the disease status was generally stable, with relatively stable performance status and low scores for prognostic indices. After combination chemotherapy, eight (62%) achieved remission. However, long-term remission was achieved in only one patient with localized lymphoma-type ATL and one young patient after allogeneic hematopoietic stem cell transplantation. In conclusion, at a center in a metropolitan and HTLV-1 non-endemic area in Japan, patients with ATL were relatively young and mainly presented with aggressive subtypes. At initial referral to our center, all 13 patients were suspected of having lymphoma but only two of having ATL. For centers in similar areas of Japan, prompt diagnosis and appropriate treatment of ATL patients will become increasingly necessary following the recent migration of HTLV-1 carriers to non-endemic areas.

Keywords: Adult T-cell leukemia-lymphoma (ATL), human T-cell leukemia virus type I (HTLV-1), non-viral-endemic metropolitan area, metropolitan region

INTRODUCTION

Adult T-cell leukemia-lymphoma (ATL) is a peripheral T-cell lymphoma associated with human T-cell leukemia virus type I (HTLV-1).[1-3] The diversity in clinical features and prognosis of patients with this disease has led to its subclassification into the following four categories: acute, lymphoma, chronic, and smoldering types.[4] The chronic and smoldering subtypes are considered indolent and are usually managed by watchful waiting until disease progression, analogous to the management of some patients with chronic lymphoid leukemia (CLL) or other lymphomas with indolent histology. Patients with aggressive ATL generally have a poor prognosis because of multidrug resistance of malignant cells, a large tumor burden with multi-organ failure, hypercalcemia, and/or frequent opportunistic infectious complications as a result of marked T-cell immunodeficiency and poor condition.[5-7] Therefore, early diagnosis and rapid referral to a tertiary hospital with hematologists is vital. Comprehensive molecular analysis revealed that many somatic alterations in ATL cells largely converged on T-cell receptor NF-κB signaling and other T cell-related pathways, and demonstrated a highly significant overlap with the Tax interactome, in addition to the frequent involvement of essential components of antigen presentation and immune surveillance.[8]

It is estimated that approximately 10 million people are infected with HTLV-1 worldwide, with endemic foci in the Caribbean basin, South America, sub-Saharan Africa, and Japan.[9,10] Japan has the highest prevalence of HTLV-1 and ATL, with approximately 1 million HTLV-1 carriers and 1000 deaths from ATL annually.[10] HTLV-1 infection is also associated with inflammatory diseases, including

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Department of Hematology, Comprehensive Cancer Center, Saitama International Medical Center, Saitama Medical University, Hidaka, Saitama, Japan
Corresponding author: Kunihiro Tsukasaki, MD, Department of Hematology, International Medical Center, Saitama Medical University, 1397-1 Yamane, Hidaka, Saitama 350-1298, Japan. E-mail: tsukasak@saitama-med.ac.jp

HTLV-1-associated myelopathy/tropical spastic paraparesis, HTLV-1 uveitis, and infective dermatitis associated with HTLV-1.[9] Although the majority of HTLV-1 carriers remain asymptomatic during their lifetime, the annual incidence of ATL among HTLV-1 carriers is approximately 60 per 100,000 carriers, with the lifetime risk being approximately 5% for men and 3% for women in Japan.[11] Epidemiological and clinical features of ATL in Japan, 2010-2011: A nationwide survey revealed that the median age at diagnosis was 68 years (interquartile range, 60-75 years) and overall, 67.2% of ATL cases were diagnosed in the Kyushu-Okinawa area.[12]

The current prevalence of HTLV-1 in Japan as determined by screening of blood donors revealed that HTLV-1 carriers were relatively rapidly aging and distributed not only in the endemic southwestern region of Japan, but throughout the country, particularly in the greater Tokyo metropolitan area.[13]

Thus far, there have been no reported case series of ATL from institutes in the greater Tokyo metropolitan area in the most recent two decades. At our metropolitan center, the International Medical Center of Saitama Medical University, we have treated 13 patients with ATL referred from neighboring clinics or hospitals since 2007. This study evaluated the diagnostic approach, clinical characteristics, and treatment outcomes of these ATL patients in comparison with those in nation-wide surveys in endemic areas.

PATIENTS AND METHODS

We evaluated a total of 13 patients with ATL who were newly diagnosed at the International Medical Center, Saitama Medical University, between April 2007 and April 2018. The total number of lymphoma patients during this period at our center was also evaluated. The cut-off date for analysis was August 2018. The diagnosis of ATL was based on clinical features, histologically and/or cytologically confirmed mature T-cell malignancy, and the presence of anti-HTLV-1 antibody.[4-6] Subtypes of ATL were classified according to the criteria established by the Lymphoma Study Group of Japan Clinical Oncology Group.[4] Clinical data included symptoms at onset with their duration, date of diagnosis, complications and laboratory/imaging data at diagnosis, therapy regimens, date of death, cause of death, and date of latest follow-up. This retrospective, nonrandomized, observational study using existing data was approved by the institutional review board and the requirement for written informed consent was waived.

RESULTS

Incidence of ATL

Thirteen patients with ATL and 1422 additional lymphoma patients were newly diagnosed at our center between 2007 and 2018. The incidence of ATL among all lymphomas diagnosed was 0.9%, which was similar to that in other HTLV-1 non-endemic areas.

Diagnostic approach at the referring clinics/hospitals (Table 1)

The time from the onset of symptoms until referral to our center by clinics and hospitals was relatively short (median, 2 months; range, 1-9 months), although one patient exhibited a chronic cutaneous lesion for 9 months before referral. At the time of referral, all patients were suspected of having at least lymphoma, mostly with lymphadenopathy. Five were examined for soluble IL-2 receptor (sIL-2R) and two were examined for anti-HTLV-1 antibody. Diagnoses of ATL were only made for two patients before referral, both of whom presented with acute ATL with leukemic manifestation; therefore, they were investigated for the presence of HTLV-1 antibody.

Table 1. Patient characteristics

No.	Age	Sex	Disease type	Stage	Initial symptom	PS	ATL-PI	Birthplace	Family history of malignancies	HTLV-Ab examination at previous hospital
1	79	male	Lymphoma	4	Lymphadenopathy	0	3	Tohoku	Mother, lymphoma	(-)
2	76	male	Acute	4	Lymphadenopathy	0	4	Kyushu	Sister, breast cancer	(-)
3	63	male	Lymphoma	4	Lymphadenopathy	1	4	Kyushu	(-)	(-)
4	58	male	Lymphoma	4	Abdominal symptoms	1	3	Okinawa	(-)	(-)
5	61	female	Lymphoma	4	Lymphadenopathy	2	5	Kyushu	(-)	(-)
6	52	male	Acute	4	Lymphadenopathy	2	4	Grandfather, Kyushu	(-)	(-)
7	70	female	Lymphoma	2	Lymphadenopathy	0	1	Mother, Kyushu	Mother, lymphoma	(-)
8	48	female	Lymphoma	4	Lymphadenopathy	2	5	not available	(-)	(-)
9	60	female	Acute	4	Malaise	1	2	not available	Mother, lymphoma	(-)
10	49	male	Acute	4	Abdominal symptoms	1	3	Mother, Kyushu	Father, prostate cancer	(+)
11	83	male	Lymphoma	1	Lymphadenopathy	2	2	Kyushu	(-)	(-)
12	64	female	Lymphoma	4	Lymphadenopathy	2	3	Kyushu	(-)	(-)
13	68	male	Acute	4	Rash	1	5	Kyushu	(-)	(+)

Abbreviations: ATL-PI, ATL-prognostic index; HTLV-Ab, human T-cell leukemia virus antibody; PS, performance status

Clinical characteristics at the time of referral (Table 2)

The median age of the 13 patients (eight male and five female) was 65 years (range, 48-83). Initial symptoms consisted of superficial lymphadenopathy in nine, abdominal fullness in two, general malaise in one, and skin rash in one. The performance status (PS) was relatively stable in most patients (range, 0-2; median, 1). In ten of the 13 patients (84%), the patient themselves or their relatives were born in Kyushu, an HTLV-1 endemic area. The places of birth were unknown for the remaining three patients. The mothers of three patients also had histories of lymphoma.

All patients were diagnosed with aggressive ATL (five acute type and eight lymphoma type); however, the disease status was generally stable with a median PS, ATL-prognostic index (PI), and Japan Clinical Oncology Group-PI of 1, 3, and 0, respectively.[14,15] sIL-2R levels were high in all patients, with a relatively wide range of 885-140,000 (median, 25,440). No patient developed complications due to opportunistic infections.

Treatment and outcomes (Table 2)

Initial treatment was a CHOP-based regimen for three, a VCAP-AMP-VECP-based regimen for six, and VCAP-AMP-VECP (mLSG15) and mogamulizumab combined chemotherapy for four depending on the year, age, and PS.[16] The response to initial treatment was summarized as complete remission in four, partial remission in four, stable disease in one, and progressive disease in four patients. However, the response duration and survival were very short for most patients, and only two patients are alive without progressive disease at the time of writing: one young patient after allogeneic hematopoietic stem cell transplantation (Patient 12) and another with localized lymphadenopathy after VCAP-AMP-VECP and mogamulizumab (Patient 7).

Table 2. Summary of the patients' characteristics

Median age, Year (Range)	65 (48-83)
Sex, Male/Female	M/F: 8/5
Disease subtypes	Acute/Lymphoma/Chronic/Smoldering: 5/8/0/0
Stage	I, II:III, IV=2:11
ATL-PI	Low/ Intermediate/ High: 3/7/3
JCOG-PI	0/1/NA: 8/4/1
sIL-2R median (Range)	25,440 (885-140,000)
1st therapy	CHOP-like/LSG15/Mog-LSG15: 3/6/4
Allo-HSCT (Yes/No)	Yes/No: 4/9

Abbreviations: Allo-HSCT, allogeneic hematopoietic stem cell transplantation; ATL-PI, ATL-prognostic index; CHOP, cyclophosphamide-doxorubicin-vincristine-prednisolone; JCOG-PI, JCOG-prognostic index; LSG15, Mog, mogamulizumab; sIL-2R, soluble interleukin 2 receptor.

DISCUSSION

This study revealed that the diagnostic approach at clinics and hospitals before referral to our institute in a metropolitan, non-HTLV-1-endemic area was relatively prompt. This resulted in no complications due to opportunistic infections or hypercalcemia with preserved PS in the 13 ATL patients even though the suspected diagnosis was lymphoma rather than ATL, as examination of anti-HTLV-1 antibody had not been performed in most cases. These early referrals resulted in early initiation of intensive chemotherapy, achieving relatively high response rates in our series.

Most of the patients presented with persistent superficial lymphadenopathy, which prompted clinicians to examine sIL-2R levels. The markedly high levels in most patients suggested lymphoma, including ATL. sIL-2R levels are relatively high in ATL, particularly in aggressive ATL, compared with in other lymphomas, probably due to shedding of the molecule from over-expressing ATL cells.[17] However, one patient (Patient 13) suspected of having indolent ATL with a massive cutaneous lesion was followed by a dermatologist for more than 6 months with only topical therapy and no blood examination due to the absence of other symptoms until progression to acute crisis.

In this series at a core hospital with a small sample size, the median age at onset of ATL was relatively young compared with that in a recent nationwide survey.[12] This survey reported a significantly younger age (median 63 year) in the Kanto region, which includes our center, compared with that in other regions, likely reflecting the younger age of HTLV-1 carriers that migrate into metropolitan areas from endemic regions, although no ATL patients were diagnosed or enrolled in the survey at our center during the survey period. All ATL cases diagnosed at our center were either the acute or lymphoma type. Possible reasons for the absence of chronic or smoldering ATL, which comprised approximately 20% of all ATL cases in the Japanese survey, include the indolent course of chronic/smoldering ATL with no symptoms or stand-alone cutaneous lesions, which may result in underdiagnosis, as in the case of Patient 13.[12]

This retrospective case series had a limited study population and may have included several biases. However, it provides preliminary but important information on the "real world" diagnosis and treatment of ATL in a metropolitan, HTLV-1 non-endemic area.

The age-standardized incidence of ATL using data from a population-based cancer registry in Japan and Surveillance Epidemiology and End Results in the US revealed that the age-standardized incidence in non-endemic areas in Japan and the US significantly increased during the study period (annual percent change [95% CI]; Japan-Honshu: +4.6% [1.1, 8.2]; US: +6.2% [1.5, 11.1]), whereas in HTLV-1 endemic areas of Japan, there was no change (annual percent change [95% CI]; Japan-Kyushu: 0.0% [-1.6, 1.7]).[18] Similarly, the current prevalence of HTLV-1 in Japan based on screening of blood donors revealed that carriers were distributed not only in the endemic southwestern region of

Japan, but throughout the country, particularly in the greater Tokyo metropolitan area.[13] These epidemiological findings suggest that ATL has been spread by carriers to non-endemic areas. Therefore, it is becoming increasingly important that rapid diagnoses are made, particularly in HTLV-1 non-endemic regions, to enable appropriate treatment of ATL patients following the recent migration of HTLV-1 carriers to non-endemic areas.[12,13,18,19]

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CONFLICT OF INTEREST

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