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Association of human T-cell leukemia virus type 1 with prevalent rheumatoid arthritis among atomic bomb survivors

A cross-sectional study

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Abstract

Previous studies have suggested that human T-cell leukemia virus type 1 (HTLV-1) might act as a pathogen in rheumatoid arthritis (RA), but epidemiological evidence of an association is scarce. We measured anti-HTLV-1 antibodies among Nagasaki atomic bomb survivors to determine whether HTLV-1 is related to RA and whether radiation exposure is associated with HTLV-1 and RA prevalence.

This is a cross-sectional study among atomic bomb survivors who participated in biennial health examinations from 2006 to 2010. Serum levels of anti-HTLV-1 antibodies were measured using a chemiluminescent enzyme immunoassay and confirmed by Western blotting. Association between HTLV-1 and RA was analyzed by a logistic regression model.

Of 2091 participants (women 61.5%; median age, 73 years), 215 (10.3%) had anti-HTLV-1 antibodies. HTLV-1 prevalence was higher among women (13.1% vs 5.8%; $P < .001$). Twenty-two participants (1.1%) were diagnosed with RA. HTLV-1 prevalence among RA participants was significantly higher than that among non-RA participants (27.3% vs 10.1%; $P = .020$). After adjustment for age, sex, and hepatitis C virus infection, HTLV-1 was significantly associated with prevalent RA (odds ratio, 2.89; 95% confidence interval, 1.06, 7.03). There was no association between radiation dose and either the prevalence of HTLV-1 or RA.

This study, among a well-defined group of atomic bomb survivors, suggests that HTLV-1 is associated with RA.

Abbreviations: AHS = Adult Health Study, ATL/ATLL = adult T cell leukemia/lymphoma, bioDMARDs = biological disease modifying antirheumatic drugs, CCP = cyclic citrullinated peptide, CI = confidence interval, CLEIA = chemiluminescent enzyme immunoassay, CRP = C-reactive protein, csDMARDs = conventional synthetic disease modifying antirheumatic drugs, Gy = gray, HCV = hepatitis C virus, HTLV-1 = human T-cell leukemia virus type 1, IF = immunofluorescent, RA = rheumatoid arthritis, RERF = Radiation Effects Research Foundation, RF = rheumatoid factor, SS = Sjogren syndrome.

Keywords: epidemiology, human T-cell leukemia virus type 1, radiation, rheumatoid arthritis

1. Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disease characterized by chronic and destructive arthritis. The prevalence of RA is approximately 0.5% to 1% of the population in developed countries,[1] including Japan.[2] RA is caused by a combination of genetic and environmental factors.

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The most important environmental factor is microbial infection, such as Epstein-Barr virus, Parvovirus B19,[3,4] and *Porphyromonas gingivalis*.[5] Human T-cell leukemia virus type 1 (HTLV-1) is a human endogenous retrovirus, and is known to be the etiological agent of adult T cell leukemia/lymphoma (ATL/ATLL) and is also associated with HTLV-1 associated myelopathy, Sjogren syndrome (SS)[6–8] and uveitis. Furthermore, an association between HTLV-1 infection and RA has been reported in several clinical and experimental studies.[9–11] Molecular mimicry has been reported as a factor in the association between microbial infection and RA incidence. In addition, HTLV-1 infects CD4 T-cells and changes cytokine release and breaks immune tolerance.[12] Recently, biological agents that directly control cytokines have been used for RA treatment. Umekita et al[13,14] reported that HTLV-1 positive RA patients had higher inflammatory markers and greater resistance to anti-TNF treatment than HTLV-1 negative patients. However, epidemiological studies measuring HTLV-1 antibodies among RA and non-RA participants remain scarce.

Another possible virus related to RA is Hepatitis C virus (HCV). It is known that HCV causes various extrahepatic manifestations, such as cryoglobulinemia, sicca syndrome, arthralgia, and fibromyalgia.[15] Dual infection with HCV and HTLV-1 may affect the course of HCV-associated disease.[16]

Many HTLV-1 infected people inhabit the southwestern area of Japan, and the virus is especially endemic in Nagasaki Prefecture. In our previous study, using immunofluorescent (IF) methods we measured anti-HTLV-1 antibodies in Hiroshima and Nagasaki atomic-bomb survivors, between 1985 and 1987.[17] The prevalence of anti-HTLV-1 antibodies in Hiroshima and Nagasaki atomic bomb survivors was 0.79% and 6.36%, respectively. An association between atomic bomb radiation and anti-HTLV-1 antibodies was not observed. We recently remeasured anti-HTLV-1 antibodies using a chemiluminescent enzyme immunoassay (CLEIA) only in Nagasaki atomic bomb survivors and detected a significant association between HTLV-1 antibodies and SS.[18]

In the present study, we investigated the association between HTLV-1 and RA prevalence in a well-defined cohort of Nagasaki atomic bomb survivors, including RA and non-RA participants with similar ages considering HCV coinfection. Furthermore, we investigated whether radiation exposure is associated with HTLV-1 and RA prevalence and determined the clinical characteristics of HTLV-1 positive RA patients.

2. Methods

2.1. Study design and participants

This is a cross-sectional study among the Adult Health Study (AHS) participants. The AHS is a clinical program for atomic bomb survivors established in 1958 by the Radiation Effects Research Foundation (RERF), formerly the Atomic Bomb Casualty Commission, as a subset of the Life Span Study cohort to examine the late effects of atomic bomb exposure.[19] The AHS biennial health examinations provide clinical information through questionnaires, physical examinations, and blood tests. It is composed of 2 cohorts: the original AHS cohort, exposed after birth and all ages; and the in-utero cohort, exposed in utero. In 2007, 645 Life Span Study participants who were younger than 10 years at exposure and lived in or near Nagasaki were added to the AHS cohort to focus on studies of radiation effects due to childhood exposure (AHS extension cohort).

Between April 2006 and December 2010, 2091 Nagasaki atomic bomb survivors (1393 from the original AHS cohort, 607 from the AHS extension cohort, and 91 from the in-utero cohort) visited RERF for routine health examinations and consented to measurement of anti-HTLV-I antibodies. In this routine health examination, participants reported their medical history, including diagnosis of RA, cardiovascular diseases, other diseases and treatment, and received hematological and biochemical examinations. Rheumatoid factor (RF), C-reactive protein (CRP) levels, and markers of HCV were measured among all participants. Anti-cyclic citrullinated peptide (CCP) antibodies were measured among the participants with suspected RA or a high titer of RF. A rheumatologist (AH) reviewed medical charts and confirmed symptoms, laboratory data, medication history, and classified RA according to the American College of Rheumatology/European League Against Rheumatism 2010 rheumatoid arthritis classification criteria.[20]

2.2. Measurement of anti-HTLV-1 antibodies, RF, CRP, anti-CCP antibody, and HCV

We tested the serum of participants for anti-HTLV-1 antibodies using a CLEIA (Fujirebio, Tokyo, Japan). When the results were positive, we confirmed the finding by Western blotting (BML, Tokyo, Japan). We defined the participants for whom anti-HTLV-1 antibody was detected by Western blotting as HTLV-1 seropositive. RF (DENKA SEIKEN, Tokyo, Japan) and CRP (SEKISUI MEDICAL, Tokyo, Japan) were measured with a latex agglutination immunoassay using an auto-analyzer (BM6010, JEOL, Tokyo, Japan). Anti-CCP antibody was tested using a CLEIA (SRL, Tokyo, Japan). Anti-HCV antibody was tested using a second-generation passive hemagglutination kit (Dynabott, Tokyo, Japan) or a second-generation EIA kit (Sysmex International Reagents Corporation, Kobe, Japan). Quantitative and/or qualitative detection of HCV RNA was also carried out using the Amplicor HCV monitor test ver. 1.0 or ver. 2.0 and/or the Amplicor HCV ver. 2.0 (Roche Diagnostics Systems, Tokyo, Japan) among anti-HCV-positive samples. Participants for whom HCV RNA was positive were defined as HCV infected.

2.3. Confirmation of vital status, cancer rate, and RA-related complications in RA patients

In order to investigate characteristics of RA patients, we examined vital status and cancer rate in RA patients. RERF follows the vital status of all AHS participants using Japan's national family registry system. Death certificates were collected for all participants who died, and the primary causes of death were recorded. The Nagasaki Prefectural Cancer Registry collects information on cancers diagnosed within the Nagasaki catchment area. We obtained information regarding vital status and incident cancer, through December 2014, using these records. We also obtained medical histories of cardiovascular diseases and RA-related complications, such as extra-articular manifestation, arthroplasty, and bone fracture, at every biannual routine health examination until 2017.

2.4. Atomic bomb radiation dose

DS02R1 weighted absorbed bone marrow doses, in gray (Gy), were estimated by the DS02 dosimetry system.[21] Briefly, the radiation dose for each participant was estimated using

geographical information (distance from hypocenter), local information (indoor or outdoor), position information (sitting or standing, direction to hypocenter), and the presence of shielding structures between the hypocenter and the individual at the time of bombing. This information excluded shielding structures was obtained from a questionnaire. Weighted doses, obtained as the sum of the gamma dose and 10 times the neutron dose, allowed for a greater biological effectiveness of neutrons. Correction for measurement error and truncation of large doses (>4 Gy) was performed. The mean and median weighted absorbed bone marrow dose was 0.286 and 0.008 Gy, respectively (range, 0–3.41 Gy). The dose distribution was highly skewed with 46% of participants in the lowest dose range <0.005 Gy and these participants were considered as a control group when we analyzed the association of radiation.

2.5. Statistical analysis

Standard descriptive statistics were used to compare participant characteristics between those with and without prevalent HTLV-1 seropositive, between those with and without a diagnosis of RA, and, among participants with a diagnosis of RA, between those with and without prevalent HTLV-1 seropositive. A standard logistic regression model estimated adjusted cross-sectional associations between participant characteristics and the odds of HTLV-1 seropositive. Due to the low prevalence of RA, a Firth bias-reduced penalized likelihood logistic regression model estimated adjusted cross-sectional associations between HTLV-1 positivity and odds of RA; this approach provides reliable estimates when the outcome is rare.[22] Models were fit among all participants and among the sub-cohort of participants with a known DS02R1 radiation dose. All analyses were completed using R 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria), including the logistf extension package.

2.6. Ethical Issues

The RERF's Human Investigation Committee reviewed and approved the study protocol (RP B43–06) on February 6, 2006, and all participants provided written informed consent.

The data will be made available by request to RERF after ethical and scientific institutional review, although we cannot publicly share the data or indiscriminately provide them upon request to protect privacy of the atomic bomb survivors.t

3. Results

3.1. Characteristics of HTLV-1 positive group and negative group

Serum anti-HTLV-1 antibodies were measured in 2091 participants (804 men and 1287 women), of whom 215 participants (47 men and 168 women) were confirmed positive by Western blotting; 223 participants were positive by CLEIA, for a false-positive rate of 4%. The prevalence of HTLV-1 infection was 10.3% (95% confidence interval [CI]: 9.0%, 11.7%) overall, 5.8% (95% CI: 4.3%, 7.7%) among men, and 13.1% (95% CI: 11.3%, 15.0%) among women. In a multivariable model, female sex and HCV infection were associated with significantly higher odds of HTLV-1 infection (adjusted odds ratio 2.34, 95% CI: 1.68, 3.33 for women, 2.17, 95% CI: 1.00, 4.28 for HCV), but there was no association of age at examination or radiation dose (Table 1).

3.2. Characteristics in the RA present group and absent group

Among 2091 participants, 22 were diagnosed with RA. The prevalence was 1.1% (95% CI: 0.7%, 1.6%). The prevalence of HTLV-1 seropositive among the RA group was 27.3% and that among the RA absent group was 10.1%. In a multivariable model including age, sex, HCV infection and cohort, HTLV-I seropositive was associated with RA (adjusted odds ratio, 2.89, 95% CI: 1.06, 7.03). There was no association of HCV or radiation dose with the odds of prevalent RA (Table 2).

3.3. Comparison between RA with and without HTLV-1 antibody

HTLV-1 positivity was associated with an older age of RA onset compared with HTLV-1 negative participants (Table 3). Age at

Table 1

Characteristics of study participants with and without HTLV-1 antibodies.

	HTLV-1 (+) N = 215	HTLV-1 (−) N = 1876	*P* value*	AOR (95% CI)†
Age, median (IQR), y	74 (69, 78)	73 (67, 78)	.032	1.17 (0.91, 1.49)
Women, n (%)	168 (78.1)	1119 (59.6)	<.001	2.34 (1.68, 3.33)
HCV infection, n (%)	10 (4.7)	42 (2.2)	.031	2.17 (1.00, 4.28)
Cohort, n (%)				
AHS original	147 (68.4)	1246 (66.4)	.32	Reference
AHS extension	63 (29.3)	544 (29.0)		1.24 (0.85, 1.80)
In-utero	5 (2.3)	86 (4.6)		0.74 (0.24, 1.86)
Radiation dose				
Unknown, n (%)	40 (18.6)	376 (20.0)	.65	–
Dose, median (IQR), mGy	6.8 (0.37, 560)	8.9 (0.60, 430)	.72	1.07 (0.76, 1.45)

AHS = Adult Health Study, AOR = adjusted odds ratio, CI = profile likelihood confidence interval, Dose = DS02R1 weighted absorbed bone marrow dose, HCV = hepatitis C virus, HTLV-1 = human T-cell lymphoma virus type 1, IQR = inter-quartile range.

* Obtained from Wilcoxon rank-sum test for continuous variables or Fisher exact test for categorical variables.

† Adjusted odds ratios of HTLV-1 infection for age (per decade), female sex, HCV infection and cohort obtained from a multivariable logistic regression model fit to all participants (n = 2091). Odds ratio for radiation dose (per gray) adjusted for age, sex, HCV infection and cohort obtained from a multivariable logistic regression model fit to participants with known DS02R1 weighted absorbed bone marrow dose (n = 1675).

Table 2

Characteristics of study participants with and without RA.

	RA present N = 22	RA absent N = 2069	*P* value*	AOR (95% CI)†
HTLV-1 (+), n (%)	6 (27.3)	209 (10.1)	.020	2.89 (1.06, 7.03)
Age, median (IQR), y	72 (69, 77)	73 (67, 78)	.97	1.00 (0.46, 2.19)
Women, n (%)	18 (81.8)	1269 (61.3)	.075	2.44 (0.92, 7.99)
HCV infection, n (%)	1 (2.5)	51 (4.5)	.43	2.65 (0.28, 11.1)
Cohort, n (%)				
AHS original	12 (54.5)	1381 (66.7)	.22	Reference
AHS extension	10 (45.5)	597 (28.9)		2.12 (0.77, 6.27)
In-utero	0	91 (4.4)		0.75 (0.01, 9.09)
Radiation dose				
Unknown, n (%)	6 (27.3)	410 (19.8)	.42	–
Dose, median (IQR), mGy	5.5 (0.33, 16)	8.3 (0.59, 430)	.31	0.80 (0.11, 2.46)

AHS = Adult Health Study, AOR = adjusted odds ratio, CI = profile likelihood confidence interval, Dose = DS02R1 weighted absorbed bone marrow dose, HCV = hepatitis C virus, HTLV-1 = human T-cell lymphoma virus type 1, IQR = inter-quartile range, RA = rheumatoid arthritis.

* Obtained from Wilcoxon rank-sum test for continuous variables or Fisher exact test for categorical variables.

† Adjusted odds ratios of prevalent RA for age (per decade), female sex, presence of HCV infection, and cohort obtained from a multivariable logistic regression model fit to all participants (n = 2091). Odds ratio for radiation dose (per gray) adjusted for age, sex, presence of HCV infection, and cohort obtained from a multivariable logistic regression model fit to participants with known DS02R1 weighted absorbed bone marrow dose (n = 1675).

examination, sex, and prevalence of RF (cut-off value: 15 IU/mL) or anti-CCP antibodies (cut-off value: 4.5 U/mL), and complication of extra-articular manifestations, arthroplasty or bone fracture, and cardiovascular diseases, and malignancies were not different between RA participants with and without HTLV-1 antibodies (Table 3). No difference in CRP/inflammatory marker at examination between the 2 groups was observed. Although HCV infection was more frequent in HTLV-1 positive participants than HTLV-1 negative participants, none of the HTLV-1 positive RA participants were infected with HCV. Treatment for RA (steroid, conventional synthetic disease modifying antirheumatic drugs: DMARDs, and biological DMARDs) at examination was not different in the 2 groups. Two cases of malignancy were identified, 1 gastric and 1 brain among HTLV-1 positive cases. One HTLV-1 positive case and 6 HTLV-1 negative cases were deceased as of the end of 2014.

4. Discussion

In this epidemiological study of an elderly population, HTLV-1 seropositivity was significantly associated with the prevalence of RA in unadjusted analysis. After adjustment for age, sex, and HCV infection, HTLV-1 seropositivity was also associated with a significant increase in the prevalence of RA. Screening of HTLV-1

Table 3

Clinical characteristics of participants with rheumatoid arthritis, with and without HTLV-1 antibodies.

	HTLV-1 positive (N = 6)	HTLV-1 negative (N = 16)	*P* value*
Age at exam, median, y	71.5	71.5	.50
Age at onset, median, y	65.5	63.0	.45
Women, n (%)	5 (83)	13 (81)	>.99
RF or CCP positive, n (%)	6 (100)	13 (81)	.53
RF titer, median, IU/mL†	53.5	101	.60
CRP, median, mg/dL‡	0.165	0.217	.58
HCV infection, n (%)	0	1 (6)	>.99
Steroid use at exam, n (%)	3 (50)	12 (75)	.33
csDMARDs use at exam, n (%)	4 (67)	12 (75)	>.99
bioDMARDs use at exam, n (%)	1 (17)	4 (25)	>.99
Extra-articular manifestations, n (%)§	2 (33)	8 (50)	.65
Arthroplasty or fracture, n (%)§	1 (17)	8 (50)	.33
Any cardiovascular disease, n (%)§	1 (17)	5 (31)	.63
Any malignancy as of 12/2014, n (%)	2 (33)	5 (31)	>0.99
Deceased as of 12/2014, n (%)	1 (17)	6 (38)	.62

bioDMARDs = biological disease-modifying antirheumatic drugs, CCP = anti-cyclic citrullinated peptide antibody, CRP = C-reactive protein, csDMARDs = conventional synthetic disease-modifying antirheumatic drugs, HCV = hepatitis C virus, HTLV-1 = human T-cell lymphoma virus type 1, RF = rheumatoid factor.

* *P* values obtained from Fisher exact tests (for binary variables) or Wilcoxon rank-sum tests (for continuous variables).

† Normal range <15 IU/mL.

‡ Normal range <0.190 mg/dL.

§ Prevalent and incident as of 2017.

antibodies in pregnant women has been performed in Nagasaki Prefecture since 1987 and the number of HTLV-1 carriers is decreasing. The strength of our study is therefore that it was possible to carry out epidemiological study of a large number of HTLV-1 carriers, which may not be possible in the near future.

An association between atomic bomb radiation and HTLV-1 prevalence was not observed, which is consistent with our previous study conducted in 1985 to 1986.[17] However, the overall prevalence of HTLV-1 seropositivity was 10.3%, which is higher than that of the previous study. The estimated prevalence of HTLV-1 was reported to be 6.2% in men and 9.4% in women among blood donors who were aged 16 to 69 years in the Kyushu area in 2006 to 2007.[23] Among 1176 participants who were HTLV-1 negative by the IF method in a previous study, 46 participants had HTLV-1 antibodies by CLEIA in the present study. HTLV-1 infects in 3 ways: mother-to-infant, sexual contact, and blood transfusion. HTLV-1 screening in donated blood was started in 1986 and infection through blood transfusion can be eliminated.[23] The elevation in prevalence occurred for 2 reasons. The first reason is infection through sexual contact. Among 46 newly detected participants, 44 were women. HTLV-1 infection by sexual contact is mainly reported to be men to women, which supports this result. The second reason is the fact that the sensitivity of the CLEIA method used in this study for HTLV-1 detection is higher than that of the IF method used in previous studies.

Although HCV infection was more frequent in HTLV-1 positive participants when compared with HTLV-1 negative participants, none of the HTLV-1 positive RA cases were infected with HCV. HCV is reported to be one of the viral pathogens associated with RA because of the lymphotropic character of this virus[15]; however, HCV was not associated with prevalent RA in the present study. The number of RA participants was small and the prevalence of HCV (2.4%) among all participants was lower than the prevalence of HTLV-1 (10.1%). Association between RA and HCV could not be clarified in these small numbers. Some reports show coinfection of HTLV-1 and HCV in the HTLV-1 endemic area, particularly among multitransfused patients[24] and HTLV-1 coinfection may affect the clinical course of HCV-related liver disease.[25] There have been no reports of HCV-related arthropathy in HTLV-1 and HCV coinfected people.

The prevalence of RA was 1.1%. This is similar to the reported prevalence in Japan[2] and other countries.[1] Furthermore, radiation was not associated with prevalent RA. This result is similar to a previous report among atomic bomb survivors.[26] Attenuation of T-cell-dependent adaptive immunity and a state of low-grade inflammation were observed in atomic bomb survivors exposed high dose radiation.[27,28] However, the association between radiation and autoimmune diseases, such as autoimmune thyroid disease[29] and SS[30] was not significant. Combined with the results of RA and HTLV-1 in this study, it is suggested that radiation-caused immunological abnormalities are not enough to cause autoimmune diseases and viral seropositivity on their own. Inflammation markers were not different in the 2 groups likely related to adequate treatment. We were unable to obtain data at RA onset and to evaluate changes of disease activity and clinical course after treatment, which are weaknesses of cross-sectional studies. Another weakness is the small number of RA patients, meaning that we could not fully investigate the characteristics of HTLV-1 positive RA patients. Among the available data, however, clear differences between RA participants with and without HTLV-1 antibody were not detected, including the rates of malignancy and cardiovascular diseases or mortality. Relative ratios of all causes of death, all cancer deaths, liver cancer, and heart diseases were significantly higher among HTLV-1 carriers when compared with non-carriers in the AHS follow-up study from 1985–1987 to 1995.[31] Higher prevalence of HCV infection is one of the reasons for higher liver cancer among HTLV-1 carriers. Recently, development of ATL/ATLL among HTLV-1 positive RA patients was reported[32]; however, none of the HTLV-1 positive RA participants were complicated with ATL/ATLL in the present study. We will continue to follow RA participants and study the effects of HTLV-1 seropositivity on morbidity and mortality.

The strengths of this study include the biennial follow-up of the unique AHS cohort with a high participation rate,[19] which contributed detailed clinical and vital information for this study. We acknowledge the following limitations. First, because this was a cross-sectional study of a population-based cohort, the number of RA cases was small. The small sample size could have limited the statistical power to detect an association between RA and HCV. Second, almost all RA participants were treated by a rheumatologist such that we could only observe the status after treatment. Third, because the information of swollen joints and overall subjective and objective symptoms using visual analogue scales were not obtained, the disease activity score was not calculated.

5. Conclusion

In this epidemiological study of measuring HTLV-1 antibodies in RA and non-RA participants, HTLV-1 seropositivity was associated with RA among atomic bomb survivors, while radiation exposure was not associated with either HTLV-1 or RA prevalence. Although the number of RA participants is small, further follow-up may clarify the natural course of HTLV-1 positive RA in the future.

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