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Atomic Bomb Radiation and Adult T-cell Leukemia

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ABSTRACT : There has been many atomic bomb survivors in Nagasaki which is also one of the endemic areas of adult T-cell leukemia (ATL). ATL is known as virus (HTLV-I) induced leukemia. Thirty-seven cases of ATL were found among the atomic bomb survivors during the period from 1950 to 1983 by reviewing their blood samples. Seventeen cases of them were developed from the cohort study samples of Radiation Effect Research Foundation (RERF). The radiation effect for the incidence of ATL was calculated using this cohort samples. Increased risk of ATL among the atomic bomb surviors could not be found in this study.

INTRODUCTION

Nagasaki is a city which has a history of exposure to the atomic bombing as well as a high incidence adult T-cell leukemia. There are still about 70,000 survivors of the Nagasaki atomic bombing. It is well known that the incidence of leukemia has incereased as a result of exposure to the atomic bomb radiation[1], while ATL is a leukemic disease caused by a virus, HTLV-I (human T-cell lymphotropic virus type I)[2]. Moreover, the infection of local residents with the virus does not seem to be a recent phenomnon ; it has been suggested that it was present more 1,000 years ago. According to an epidemiological investigation, 5-10% of the adults of the Nagasaki region are carriers of HTLV-I[3].

It is of grest interest medically to investigate how individuals are affected when two specific carcinogenic factors, that is, exposure to the atomic bombing and infection with HTLV -I, act on an individual. Therefore, we examined patients with ATL selected from atomic bomb survivors. Our findings did not suggest that the incidence of ATL was significantly higher in atomic bomb survivor than in controls. However, it seems that we are not the only ones who have an interest in the combination of these two carcinogenic factors. We have received inquires about our investigation several times. For this reason, we decided that it is necessary to report the results of the present study, even though they are negative.

SUBJECTS AND METHOD

The Department of Internal Medicine, Atomic Disease Institute, Nagasaki University School of Medicine and the Radiation Effects Research Foundation (RERF) have carried out a collaborative study on leukemia, leukemic malignant lymphoma and associated diseases occurring in and outside Nagasaki City since around 1950. The diseases were detected by conducting a leukemia registration program, confirming diagnosis by obtaining blood samples and carrying out a continuous investigation concerning the occurrence of these diseases in the atomic bomb

survivors.

In order to identify ATL cases among atomic bomb survivors based on the registry data, one of the aurthors of this report, M. Ichimaru, reexamined blood samples from the registered cases. ATL was confirmed by conducting morphogical observation of the leukemia cells and by studying the clinical charts. Since most of the cases were from the past, data concerning anti-HTLV-I antibody was unavailable except for a few recent cases.

In order to analyze the relationship between atomic radiation dose and the incidence of ATL, we examined the 30,761 atomic bomb survivors in the RERF extended life span study cohort for whom dose estimates were available, and we evaluated the results statistically.

The atomic bomb radiation dose estimates eatablised in 1965 (T-65D) were used[4]. Although the radiation dose in Hiroshima and Nagasaki has been reconsidered on an extensive scale in recent years and a new dosimetry system, DS86[5], is now in use, the Nagasaki dose estimates do not differ widely between T-65 and DS86. Therefore, the T-65 doses were used for convenience in out study.

RESULTS

In the study period ending December, 1983, 37 patients suspected to have ATL were found among the atomic survivors in Nagasaki as a result of the examination of blood samples from all the cases with leukemia and leukemic malignant lymphoma.

1. The relationship between ATL and exposure to the atomic bombing in the 37 ATL cases.

Table 1 shows the distribution of the 37 ATL cases by sex, age, the period of onset by distance from hypocenter and sample classification by sex to determine whether or not these 37 cases belong to the FERF fixed cohort. The ratio of male to female was 3 : 2, and 35% of the cases were in their 50 years, cleary reflecting the characteristics of age structure of ATL. Looking at the distribution by distance from the hypocenter, 11 cases were proximal survivors (less than 2.5Km), and 26 distal survivors. For both proximal and distal survivors, the number of

Table 1. Distribution of ATL cases in a-bomb survivors in Nagasaki by sex, age, distance and sample classification, as of Dec. 1983

Age at onset	Sex		Total
	Male	Female	
<40	3	3	6
40−49	7	2	9
50−59	7	6	13
60−69	2	4	6
70+	2	1	3
Total	21	16	37
Year of onset	Distance from the hypocenter (m)		Total
	<2.5Km	2.5−9.9Km	
1950−1960	2	2	4
1961−1970	2	9	11
1971−1980	5	10	15
1981−1983	2	5	7
Total	11	26	37
Sex	Sample classification		Total
	LSS Extended Sample	others	
Male	8	13	21
Female	9	7	16
Total	17	20	37

LSS: life span study

Table 2. Crude incidence rate of ATL in a-bomb survivors in LSS extended sample in Nagasaki, 1950-1983

Items	T65DR total dose (rad)				Total
	0	1-49	50-99	100+	
		Oct. 1950-Dec. 1960			
Person years (PY)	149018	109107	14261	27104	299490
Case	0	2	0	2	4
Rate (10^{-5})	0.0	1.8	0.0	7.4	1.3
		Jan. 1961-Dec. 1970			
PY	129023	95522	12713	24304	261562
Case	5	2	0	0	7
Rate (10^{-5})	3.9	2.1	0.0	0.0	2.7
		Jan. 1971-Dec. 1983			
PY	144764	108009	14327	27766	294866
Case	2	4	0	0	6
Rate (10^{-5})	1.4	3.7	0.0	0.0	2.0
		Oct. 1950-Dec. 1983 (total period)			
PY	422804	312638	41301	79175	855918
Case	7	8	0	2	17
Rate (10^{-5})	1.7	2.6	0.0	2.5	2.0

Note: Excluding unknown dose

Table 3. Summary of regression analysis and analysis of dose effect for ATL incidence in a-bomb survivors in LSS extended sample in Nagasaki, 1950-1983

1. Relative risk model
$\lambda_S = \lambda_{os}(1+\beta_1 D)$
Strata = Sex, 3 age ATB group (0-19, 20-39, 40+)
D = 4 dose group (0, 1-49, 50-99, 100+)
Parameter

Name	Esitimates	S. E.
Dose (β_1)	0.3229E-3	0.3057E-2
Test of dose effect: $\chi^2 = 0.01$ [1]		N. S.

2. Relative risk model with multiplicative risk function (Loglinear model)
$\lambda = e^{\beta_0+\beta_1 Sex+\beta_2 log\cdot ageATB+\beta_3 Dose}$
Parameter

Name		Estimates	S. E.
Constant	(β_0)	-13.26	1.166
Sex	(β_1)	0.3612	0.4880
Log Age ATB	(β_2)	0.7444	0.3403
Dose	(β_3)	0.4728E-3	0.2778E-2
Test of dose effect: $\chi^2 = 0.028$ [1]			N. S.

3. Additive model
$\lambda = e^{\beta_0+\beta_1 Sex+\beta_2 log\cdot ageATB}+\beta_3 Dose$
Parameter

Name		Estimates	S. E.
Constant	(β_0)	-13.35	1.221
Sex	(β_1)	0.3915	0.4989
Log Age ATB	(β_2)	0.7636	0.3511
Dose	(β_3)	0.1600E-7	0.6321E-7
Test of dose effect: $\chi^2 = 0.080$ [1]			N. S.

ATL cases tends to increase in recent years.

The 17 cases of these 37 cases belongimg to the RERF fixed cohort (LSS extended sample) were used to examine the relationship between atomic bomb radiation exposure and incidence of ATL.

2. Incidence rates of ATL in the fixed cohort.

Table 2 shows the annual crude incidence rates of ATL (per 100,000) by three periods and by dose. Looking at the rates in the three periods, the number of cases shows a decrease, but the 2 cases with relatively high dose (more than 1Gy) were from the period between 1950 and 1960.

Table 3 shows a summary of the regression

Appendix List of ATL cases in Nagasaki a-bomb survivors until Dec. 1983

M. F. #	Sex	Onset		Distance (m)	LSS extended Sample
		Age	Month - Year		
008-237	F	52	9 - '67	5887	—
009-812	M	56	9 - '58	1152	Yes
014-489	F	56	4 - '79	2525	Yes
015-885	M	54	8 - '69	3056	—
017-420	F	29	12 - '57	2600	Yes
017-551	M	54	2 - '68	4137	Yes
019-286	F	57	1 - '77	2712	Yes
021-326	F	65	11 - '79	3209	—
029-711	M	51	1 - '61	3591	Yes
030-702	M	56	5 - '76	5027	—
032-402	F	58	6 - '80	2049	Yes
047-441	M	58	3 - '72	2882	—
050-624	M	42	7 - '75	3845	—
056-535	M	76	8 - '68	3186	Yes
066-168	M	63	2 - '82	3651	—
066-560	M	49	11 - '83	3178	Yes
085-466	M	25	8 - '55	2537	Yes
089-804	F	55	6 - '68	1761	Yes
089-834	F	29	7 - '56	1311	Yes
092-313	F	37	4 - '73	2394	Yes
097-494	F	75	11 - '80	3201	—
100-852	F	46	12 - '77	4680	—
102-764	M	57	10 - '68	3812	Yes
106-227	M	69	10 - '65	4699	Yes
137-854	F	65	9 - '67	2817	Yes
165-217	F	69	8 - '74	0682	Yes
623-599	M	41	2 - '76	8502	—
624-773	M	40	11 - '83	2000*	—
662-918	F	50	12 - '79	2193	—
733-778	M	31	7 - '62	5152	—
748-969	M	38	5 - '68	4438	—
761-454	F	46	7 - '75	1563	—
774-167	M	47	5 - '80	8492	—
776-735	M	46	7 - '81	2500*	—
777-368	M	47	3 - '82	5000*	—
778-261	F	65	1 - '82	4000*	—
780-734	M	70	4 - '81	1500*	—

* Distance information from Dept. of Hematology Nagasaki Medical School.
M. F. # : Master file number of RERF

analysis of dose effects on three statistic models using all the cases divided into three age groups (0-19, 20-39, 40+) to determine whether or not exposure to the atomic bombing affects the incidence of ATL. According to our results, no significant differences in dose effect were found in any of the three modeles. We concluded that exposure to atomic bomb radiation does not appear to have had an effect on the incidence of ATL.

DISCUSSION

It has been found that the incidence of leukemia increased in proportion to the radiation dose among atomic bomb survivors in Hiroshima and Nagasaki. Although it is clear that exposure to the atomic bombing affected the incidence, the biological mechanism linking exposure to radiation to the incidence of leukemia has not been elucidated.

Leukemia occurred in only a very limited number of atomic survivors even when they had been exposed to the same amount of radiation. This suggests that several factors in addition to the aberration of cells due to the exposure to radiation are involved in the onset of leukemia. Little has been known about these factors. However, the existence of a virus that activates genes has been cited as a possible factor. Nagasaki underwent the explosion of a plutonium atomic bomb and is also a densely infected area of HTLV-I, which is suspected as a cause of ATL. It seemed important to investigate the incidence of cancer when two influential carcinogenic factors, that is, exposure to radiation and infection with a carcinogenic virus, coexist in the same population. From this point of view, we studied the relation between radiation exposure and ATL in atomic bomb survivors. In our study, however, there was no evidence that atomic survivors have a higher incidence of ATL due to the exposure to radiation. The following are problems involved in this study.

First, ATL was diagnosed by morphological observation of aberrant cells in blood samples. Although our diagnosis are not absolutely certain, it seems quite possible to diagnose old cases with rather high reliability considering the characteristics of aberrant cells, because ATL cells show distinct morphological features and anti-HTLV-I antibody was positive in 100% of the ATL cases diagnosed by cell morphology in Nagasaki[6]. Lymphoma-type ATL was not detected in this study because aberrant cells hardly appear in the peripheral blood. In the past it was probably considered to be malignant lymphoma. Considering the fact that there was no evidence of a marked increase of malignant lymphoma among the Nagasaki atomic bomb survivors[7], it is unlikely that only this type of ATL increased. The relatively small number of ATL cases found between 1950 and 1960 is possibly due to the fact that we started our leukemia registration program in 1959.

Studies equally as deteiled as our investigation of leukemia seemed to support the conclusion that there is no increase of ATL cases in proportion to the amount of radiation dose. That is, the combined influence of atomic radiation and HTLV-I in carcinogenesis was not evident.

The following also lends credibility to our conclusion. It is possible that radiation in the incidence of leukemia affects the bloods cells on a different level than HTLV-I in the incidence of ATL. The study of leukemia induced by atomic bomb radiation suggests that radiation affects hematopoiectic stem cells, which causes the onset of leukemia in many cases. In ATL, on the other hand, HTLV-I infects to differenciated T-cells (helper T-cells), and T-cells are transformed into tumor cells[8], which causes the onset of ATL. The difference in levels of blood cells of leukemogenesis might be the reason for why the incidence of ATL have not been increased among atomic bomb survivors. However, it is a fact that chromosome aberrations apparently caused by radiation are frequently observed in the peripheral T-cells of atomic survivors[9]. Moreover, there are other types of cancer which show an increase of incidence in a different period from leukemia[10]. These facts indicate the necessity to wait for future observations before making a final conclusion.

CONCLUSION

We examined the question of whether or not ATL occurring in HTLV-I carriers increases among the atomic bomb survivors in Nagasaki, but no such evidence was found in the cases up to date.

Dedicated to the late Dr. Toranosuke Ishimaru, co-author of this paper, who passed away suddenly after completing the data on the statistic analyses for this paper.

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