II. BIOLOGICAL EFFECTS

Atomic Bomb and Leukemia

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Atomic bomb/Leukemia/Threshold/FAB classification/Chromosome
Characteristic features of leukemia among atomic bomb survivors were studied. The ratio of a single leukemia type to all leukemias was highest for CML in Hiroshima, and the occurrence of CML was thought to be most characteristic for atomic bomb radiation induced leukemia. In the distribution of AML subtypes of FAB classification, there was no M3 cases in 1Gy or more group, although several atypical AML cases of survivors were observed. Chromosome study was conducted using colony forming cells induced by hemopoietic stem cells of peripheral blood of proximal survivors. Same chromosome aberrations were observed in colony forming cells and peripheral blood of proximal survivors.

INTRODUCTION

The leukemias that occurred among atomic bomb survivors are one of the important model of the radiation induced human leukemia. There are some differences among the atomic bomb induced leukemia, so-called secondary leukemia and de novo leukemia. We shall describe some characteristic features of the leukemias which were probably induced by atomic bomb radiation. The effect of atomic bomb radiation on human body was mainly due to simple whole body irradiation.

The bone marrow of proximally exposed survivors became aplastic by heavy dose of radiation, however, the reproduction of new blood cells in the bone marrow was already seen in proximally exposed persons who died about 2 months after the bomb. The leukemia occurred among those exposed persons whose blood cells had recovered to a normal count after the bomb.

Leukemia cases among atomic bomb survivors increased gradually from 1946, and the peak of occurrence was observed about 6 years after the bomb[1].

Fig. 1 shows the number of cases and types of leukemia in Hiroshima and Nagasaki among those who received 0.01Gy or more.

There are some differences in leukemia type between the two cities. The ratio of chronic myelogenous leukemia (CML) to all leukemia is significantly higher in Hiroshima than in Nagasaki. The risk of all types of leukemia increases with dose in both cities, except for Nagasaki survivors who received less than 1Gy Kerma total dose (average marrow dose). This difference between two cities is clearly observed in CML incidence, but is not so clear in acute leukemia. Accordingly, this difference seems to be due to the difference in CML incidence between the two cities. The
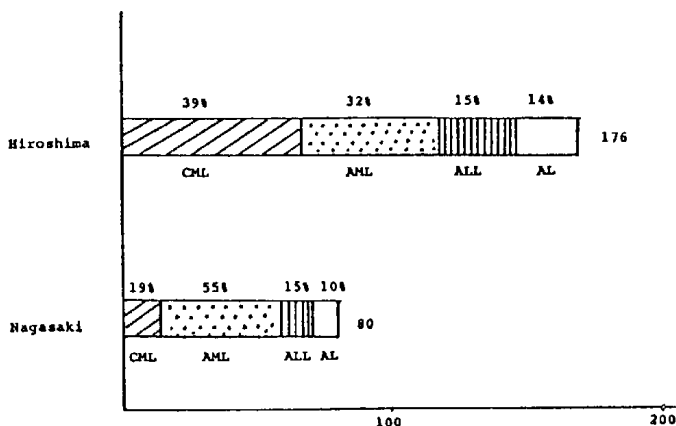
Fig. 1. Cases and type of leukemia among atomic bomb survivors who received
0.01Gy or more (1945-1975).

risk of CML in Hiroshima increases from individuals who received less than 0.5Gy Kerma total
dose, but no increase in Nagasaki in this dose. Another important point of atomic bomb induced
leukemia is that leukemogenic risk has been higher among the survivors who were younger at
atomic bomb in earlier stage. This tendency is most clear in CML cases[2].

The apparent threshold of acute leukemia and CML was reviewed using the leukemia samples
of Hiroshima.

The features of CML in Hiroshima are most characteristic to atomic bomb radiation induced
leukemia. This increased incidence of CML is much different from so-called secondary
leukemia[3].

The peak of the occurrence of CML was observed 6 years after the bomb also in the below
1Gy group as in the 1Gy or more group. Accordingly, there might be radiation effect to induce
CML occurrence in the below 1Gy group also. The same phenomenon of CML was observed
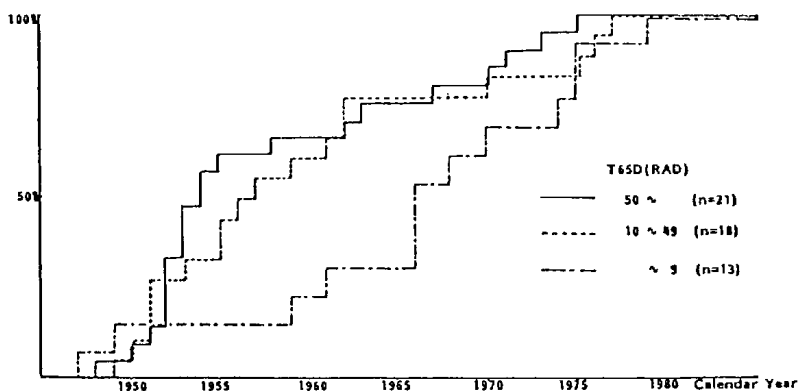in three groups of 0.5 or more, 0.1~0.49 and below 0.09Gy (T65D dosimetry).

Fig. 2. Cumulative Cases of Chronic Myelogenous Leukemia by Radiation Dose.
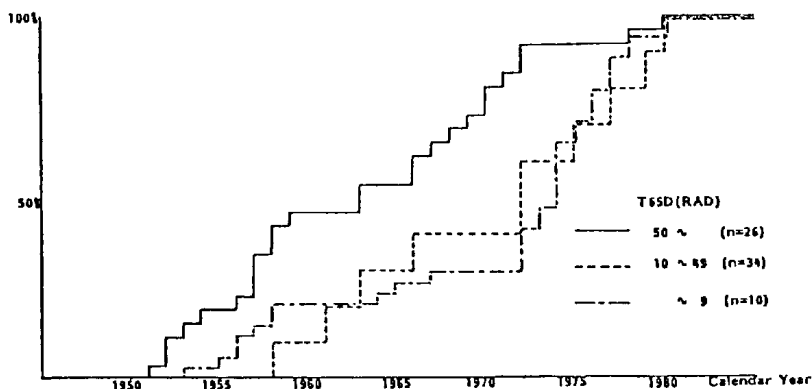
Fig. 3. Cumulative Cases of Acute Myeloid Leukemia by Radiation Dose.

Fig. 2 shows the percentage of cumulative CML cases in each year from 1946 to 1980.

The shape of occurrence curve is the same in the 0.5Gy or more and 0.1∼0.49Gy groups, but different in the below 0.09Gy group. Therefore, it is suggested that an apparent threshold of CML occurrence is between 0.5 and 0.09Gy.

On the other hand, the shape of acute leukemia in the 0.1∼0.49Gy group was similar to that in the below 0.09Gy group as shown in Fig. 3.

When acute leukemia cases in Hiroshima are divided into two groups by exposure dose (1Gy or more and below 1Gy), there is no peak of occurrence unlike CML in the lower dose group. These findings suggest that the apparent threshold of acute leukemia occurrence may be near 1Gy.

Therefore, it was suspected that the characteristic feature of A-bomb induced acute leukemia might be in the cases who received 1Gy or more.

Recently, blood samples of leukemia cases among atomic bomb survivors have been reviewed by FAB (French-American-British) classification. The review has been completed for about 65% of the cases[5].

As shown in Table 1, ALL and MDS increased compared with the control group in 1Gy or more group. CML increased in 1Gy or more and 0.01∼0.99Gy groups. In the distribution

Table 1. Leukemia Types by FAB Classification and Radiation Dose (both cities combined)

	T65D		
	0 Gy	0.01–0.99 Gy	1 Gy
AML	120 (65.9%)	49 (45.8%)	33 (31.7%)
ALL	20 (11.0%)	15 (14.0%)	27 (26.0%)
MDS	10 (5.5%)	4 (3.7%)	13 (12.5%)
CML	32 (17.6%)	39 (36.5%)	31 (29.8%)
Total	132 (100%)	107 (100%)	104 (100%)

Table 2. Distribution of AML Subtypes by FAB Classification (Atomic Bomb Survivors)

	0 Gy	T65D 0.01–0.99 Gy	1 Gy
M1	33	11	12
M2	30	12	7
M3	16	9	0
M4	20	8	6
M5	10	1	1
M6	8	2	1
Total	117	43	27

by age at bomb, the ratio of AML and ALL of below 15 years of age was largest. In the distribution of AML subtypes, there was no M3 case in the 1Gy or more group. (Tab. 2)

In general, there is no specific difference between AML of the survivors and de novo AML.

However, we find some non typical and interesting cases in survivors' acute leukemia. We would like to describe some of those cases.

The 1st case was diagnosed as aplastic anemia six years after the bomb (estimated dose was 3.81Gy). Severe pancytopenia and general hypoplastic marrow, but partial blast cell proliferation was found in marrow which suggests an existence of leukemia.

The 2nd case suffered from severe progressive anemia in 1952, and died 3 months after. Estimated dose was 2.79Gy. Autopsy revealed diffuse bone marrow fibrosis and immature cell infiltration in the liver and kidney.

The 3rd case was admitted because of malaise and fever 20 years after the bomb. Lymphonode swellings and hepatosplenomegaly were noticed. Bone marrow was dry tap. The estimated radiation dose was 1.63Gy. The patient died after 6 months. The autopsy diagnosis was acute leukemia and malignant myeloskerosis. Immature cell infiltration was observed in the liver and kidney.

The 4th case developed acute leukemia with hepatosplenomegaly 16 years after the bomb. The estimated dose was 1.29Gy and the patient had severe anemia and thrombocytopenia. The

Table 3. 5 Cases of Atypical Leukemia and Their Peripheral Blood

Case	Age, (age ATB)	Dose (Gy)	RBC $\times 10^4$	WBC	Plate $\times 10^4$	Blast (%)
1. K.K.	51 (45)	3.81	54	3200	1.2	0
2. C.M.	22 (15)	2.79	77	3900	1.3	5
3. M.I.	39 (19)	1.63	270	3000		1
4. Y.I.	31 (14)	1.29	201	9700	8.0	3
5. M.H.	59 (39)	2.49	91	5200	9.6	5

appearance of erythroblasts and megakaryocytes with myeloblasts were observed in peripheral blood.

A bnormal immature cell proliferation of three blood series was observed in the bone marrow. The diagnosis was acute panmyelosis.

The 5th case was diagnosed to have acute myelogenous leukemia 20 years after the bomb with an estimated radiation dose was 2.49Gy. Abnormal proliferation of three blood series was also recognized in the bone-marrow. (Tab. 3)

As stated above, the increase of CML, the feature of leukemia types by FAB classification, and the cases of acute leukemia with abnormal findings in three blood series suggest that the initial leukemogenic effect of the atomic bomb radiation occurred in hemopoietic stem cells.

CHROMOSOME STUDY

Finally, we would like to describe the chromosome aberrations in atomic bomb survivors.

Even now, significantly increased chromosome aberrations due to atomic bomb radiation are recognized in peripheral blood T-cells[6] and bone marrow cells in proximally exposed atomic bomb survivors. Chromosome study was performed using colony forming cells induced by hemopoietic stem cells of peripheral blood of proximally exposed survivors whose chromosome aberrations were confirmed in peripheral blood T-cells[7]. The same chromosome aberrations in colony forming cells and peripheral T-cells were observed in several survivors (Fig. 4).

This also suggests that atomic bomb radiation affected hemopoietic stem cells and these cells differentiated to peripheral T-cells.
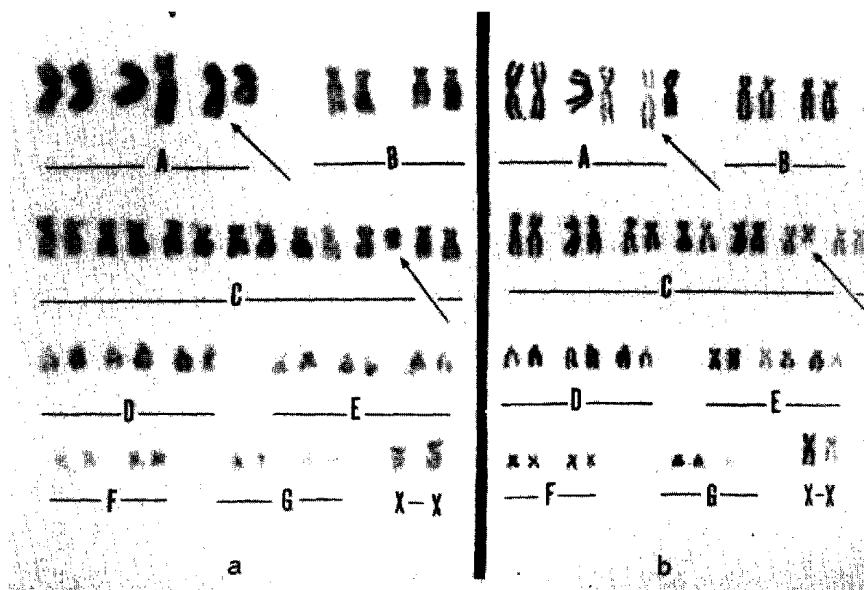

Fig. 4. Abnormal karyotypes 46,XX,t(3q + ;Cq−) seen in (a) a circulating burst and (b) peripheral T-lymphocyte of an atomic bomb survivor. They closely resemble each other.

CONCLUSION

1) There were some qualitative differences in leukemia type among atomic bomb survivors between Hiroshima and Nagasaki.

2) The risk of chronic myelogenous leukemia was higher in Hiroshima than in Nagasaki. This increase of CML may be the different feature of atomic bomb survivors' leukemia from the so-called secondary leukemia.

3) There was no remarkable difference in feature between the leukemia of atomic bomb survivors and de novo leukemia, although several non-typical cases have been observed.

4) In 1Gy or more group, ALL and MDS increased compared to the control group, and there was no M3 case in the distribution of AML subtypes (FAB classification).

5) The apparent threshold of CML occurrence in Hiroshima might be between 0.5~0.09Gy, and that of acute leukemia near 1Gy.

6) Same chromosome aberrations were observed in both colony forming cells induced from stem cells as well as in the peripheral T-cells suggesting that the initial leukemogenic effects of atomic bomb radiation was in hemopoietic stem cells.

The present report is based upon T65D estimated doses[8].

ACKNOWLEDGMENTS

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