Hematological Studies of Six Cases of Accidental Exposure to an Iridium Radiographic Source

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ABSTRACT

Among six persons (male, age 20-30) exposed accidentally to $^{192}$Ir gamma-rays, five cases showed hematopoietic disorders of various degrees. One case (S. H. 25 Yr.) showed a severe hematopoietic injury such as pancytopenia between the 3rd and 7th week after the initial exposure. On the 4th and 5th week, thrombelastogram showed an earliest and significant improvement, followed by increase of leukocyte and platelet counts. This clinical test was useful for diagnosis and prognostic evaluation in this crucial pancytopenic period during which some treatments or cares were needed. He was treated only with a prophylactic administration of antibiotics in an isolated clean aseptic room. Since 5th week, the hematopoietic disorders were rapidly improved although the leukocyte counts still remained at a subnormal level for more than 18 months. The other 4 cases showed various degrees of temporal leukopenia and hypoplasia of bone marrow, while neither anemia nor thrombocytopenia was observed.

From the severity of hematopoietic disorders, a dose delivered to hematopoietic organs of S. H. was estimated to be somewhat between 200 and 400 rad. This was different from a cytogenetically estimated dose of 124 rad. The difference may mainly reflect a difference of doses received between hematopoietic cells and of peripheral circulating lymphocytes, which might be resulted from a different distribution of these cells in the body and from a non-uniform gamma-rays irradiation of $^{192}$Ir source.

INTRODUCTION

Six non-occupational males, aged 20-30 were accidentally exposed by the gamma-ray from $^{192}$Ir source (5.3 Ci) which was picked up in a shipyard at Ichihara, Chiba, Japan on 18th September, 1971 and brought to their lodging-house by one of them. They were irradiated by the source during 7-8 days in various degrees. The history of this accidental exposure was described in details on the other related paper.\(^1\)
Three cases of them showed the gamma-rays burns such as painful erythema, blisters and ulcers of hands or buttocks which were contacted with $^{192}$Ir source. Five cases of them showed the hematopoietic disorders in various degrees. Some of them showed the disturbances of spermatogenesis. The details of clinical observations were reported elsewhere.$^{2}$ On the present paper, the disturbances of hematopoiesis in these cases were described and discussed in details.

MATERIAL AND METHODS

These six men, aged 20-30, were admitted to the Hospital of National Institute of Radiological Sciences, Chiba, Japan since eight days (4 cases; S. H., M. K., T. S. and M. I.) and nine days (one case; Y. S.) and 24 days (one case; K. J.) after the presumed starting date of the exposure.

In the course of treatment, S. H. was isolated into a clean aseptic room between the 32nd and 65th day. Three cases of them (M. I., M. K., T. S.) on the 59th day, K. J. on the 70th day, S. H. on the 132nd day and Y. S. were discharged from the hospital on the 188th day. Thereafter, they are examined periodically as out-patients.

Hematological measurements were carried out by standard manual methods. Platelets were counted by the method of Brecher and Cronkite. Reticulocyte count was measured by Brecher's method.$^{3}$

Serial studies of aspirated bone marrow were performed. The bone marrow was aspirated from different sites, usually from the sternum, anterior iliac crest and posterior ilium. Sometimes, two different sites i.e. sternum and anterior iliac crest or sternum and posterior ilium were examined simultaneously.

Using the machine of thrombelastograph (Helighe Co.), $m$ a. (Maximale Amplitude), $r$ (Reaktionszeit) and $K$ (Koagulationsgeschwindigkeit) in whole blood were measured on thrombelastogram.$^{4}$

RESULTS

Among six persons, only one case (M. I.) showed no hematological disorders. The other five cases revealed the various degrees of hematopoietic disturbance by external irradiation. Especially, one case (S. H.) showed the severe thrombopenia and leukopenia combined with moderate anemia between the 3rd and 7th weeks after the presumed starting date of the exposure.

I. Hematological changes in a severe case (S. H.)

A man aged 25 years, was first examined 8 days after the initial exposure of $^{192}$Ir. He had nothing of importance in the past history and family history before this accident. His general condition was quite well when he was hospitalized. Hematological data in this time showed only a moderate leukopenia (3,300/mm$^3$) with lymphopenia (800/mm$^3$). Hemoglobin concentration was 14.8 gr./dl, red blood cell count 4,320,000/mm$^3$ and platelet count was 240,000/mm$^3$.

Time course studies on the changes of circulating blood were summarized in
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Fig. 1. He also showed the gamma-rays burns of both hands such as transient erythema, blisters resulted in atrophy and scarring of the skin.

(1) Erythropoiesis; The hemoglobin (Hb), red blood cell (R.B.C.) and hematocrit (Hct.) decreased gradually and reached the lowest at the 39th day. (Fig. 1 and Table 1.) Before this period, the depression of reticulocyte production was remarkable. The lowest reticulocyte value was observed at the 23rd day. (Fig. 1 and Table

![Fig. 1. Hematological changes in S. H. Case](image)

**Table 1.** Hematological data in the critical stage of S. H. case. The underlined figures mean the lowest values in each items.

| Days after Exposure | Hct. (%) | Hb. (gm./dl) | RBC (million/mm³) | WBC (per mm³) | Platelets (thousands/mm³) | Retics (%) | Thromb. elastogram m. a. (mm) |
|---------------------|---------|--------------|--------------------|---------------|--------------------------|-------------|-------------------------------|
| 20                  | 41      | 12.0         | 4.10               | 4400          | 110                      | 0.75        |                               |
| 23                  | 40      | 12.0         | 4.14               | 3900          | 50                       | 0.04        |                               |
| 25                  | 38      | 11.6         | 4.08               | 3400          | 50                       | 0.10        | 34.5                          |
| 27                  | 39      | 11.4         | 3.96               | 3400          | 35                       | 0.10        |                               |
| 30                  | 34      | 11.0         | 3.66               | 1100          | 15                       | 0.25        |                               |
| 32                  | 32      | 9.6          | 3.45               | 800           | 20                       | 0.30        | 43.0                          |
| 34                  | 31      | 9.9          | 3.31               | 800           | 20                       | 0.70        | 48.0                          |
| 37                  | 29      | 9.2          | 3.14               | 1000          | 40                       | 1.15        |                               |
| 39                  | 28      | 8.6          | 2.95               | 1000          | 80                       | 2.30        | 47.0                          |
| 41                  | 29      | 9.3          | 3.23               | 1300          | 140                      | 1.90        |                               |
| 44                  | 31      | 10.0         | 3.20               | 1400          | 140                      | 4.40        |                               |
| 48                  | 31      | 10.2         | 3.35               | 1500          | 200                      | 4.45        |                               |
1) Mean corpuscular hemoglobin (MCH) was constant in normal range.

2) Leukopoiesis; An early lymphopenia developed and persisted between the 9th and 51st day. The absolute lymphocyte counts in this period ranged from 300 to 900/mm³. The total white blood cell (W.B.C.) count was decreased rapidly until the 11th day. After the first dip of W.B.C. count (1,600/mm³) at this time, it increased temporarily and thereafter it reached the lowest value (800/mm³) at the 32nd day. Therefore, the time course of W.B.C. showed a biphasic pattern and the existence of abortive rise was remarkably demonstrated in this case. (Fig. 1) These changes of W.B.C. counts was mainly due to the variation in the number of neutrophils. In 3rd to 7th week, the severe decrease of neutrophils was observed.

3) Thrombopoiesis and hemorrhagic disorders; Platelet counts dropped very rapidly and reached the lowest value (15,000/mm³) on the 30th day. (Fig. 1 and Table 1) The remarkable prolongation of bleeding time (over 10 minutes) was observed since 19 days after the initial exposure. However, the other values of the examination on hemostasis including coagulation time, one-stage prothrombin time (Quick), recalcification time test, fibrinogen concentration, euglobulin lysis time, partial thromboplastin time test and capillary resistance test were almost in normal range and clinical symptoms of hemorrhagic tendency such as petechiae and gingival bleeding etc. were not observed in this period. However, the interesting observations were performed on the thrombelastogram. On the 25th day, the value of m. a. (Maximale Amplitude) was remarkably decreased (34.5 mm) compared with normal values (47.0-55.0 mm). While the platelet counts dropped into minimum on the 32nd day, the value of m. a. recovered already. (Table 1)

4) The change of bone marrow; The first examination of bone marrow was done at 9 days after the initial exposure. The sample showed remarkable hypocellularity and a diminution in three cell lines were noted while plasma cells and reticulum cells remained. (Photo 1) The time course studies on the changes of sternal myelogram was summarized in Fig. 2. The changes of peripheral blood, such as leukocyte and reticulocyte were well corresponded to that of myelogram. (Fig. 2) Mitotic indices (M.I.) were low both in myeloid and erythroid immature cells.

5) Morphological changes of hematopoietic cells; The degenerative figures of hematopoietic cells were remained more than 3 months after the initial exposure. The types of degeneration were vacuolization of cells, appearance of 'toxic granulae' and swelling of nuclei. The other types of anomalies, such as giant neutrophils, binucleated lymphocytes etc. were not observed.

6) Recovery pattern of hematopoiesis; As described before, the lowest values of reticulocytes, platelets, leukocytes, erythrocytes, hemoglobin concentration and hematocrits were observed 23, 30, 32, 39, 39 and 39 days after the initial exposure respectively. (Table 1) Especially, between the 30th and 40th days, the increased susceptibility to infection and hemorrhage due to leukopenia and thrombopenia was considered. The precautionary use of minimum dose of antibiotics and the isolation to a clean asptic room were applied. The recovery of platelet counts preceded the
other cell lines. Platelet level actually rose to normal on the 48th day. Anemia was improved until the 95th day while the recovery of leukopoiesis was delayed and leukocyte counts remained subnormal over 18 months after the initial exposure. The recovery of bone marrow occurred partially. (Photo 2) Some differences between the sites of aspiration were noted. In general, the cellularity of the aspirates from posterior ilium was more than that of sternum. Photo 2 showed the form of recovery. Among the hypoplastic area, the active hematopoietic island were observed. The increase of mitotic indices was observed earlier in erythroblasts than myeloid
precursor cells.

II. Hematological changes in five other cases;

Total neutrophils and lymphocyte counts in blood of five cases compared with S.H. was shown in Fig. 3. The recovery pattern of granulocyte in five case was quite different from S.H. case. The abortive rise in the 3rd week was not observed in these cases.

One person, M.I. (24 Yr.) showed no hematological disorders in a whole our observation period. Two cases, M.K. (24 Yr.) and T.S. (30 Yr.), showed leukopenia which reached minimum values at 11 days after the initial exposure. Erythropoiesis and thrombopoiesis of them were completely normal. The lowest values of leukocytes were 2,700/mm³ for M.K. and 3,300/mm³ for T.S. respectively. Corresponding with these changes in blood, bone marrow showed slight (T.S.) or moderate (M.K.) degrees of hypoplasia with relative increase of plasma and reticulum cells. W.B.C. counts of these cases were completely normalized since about 20 days after the initial exposure. The overshooting figures of regeneration in bone marrow were observed until nearly 60 days for M.K. and 20 days for T.S. after the initial exposure.

One case, Y.S. (20 Yr.), who suffered from severe radiation burns such as erythema, blisters and ulcers of hands and buttocks which were contacted with ¹⁹²Ir source, was admitted at 9 days after the initial exposure.

Hematological data in this time revealed only a moderate leukopenia (3,500/mm³) with lymphopenia (840/mm³). No anemia and platelet count was 290,000 mm³. W.B.C.
count decreased until 11 days after the initial exposure and the lowest value of W.B.C. was 2,700/mm³. Thereafter, W.B.C. increased with fluctuating waves and reached normal value on the 25th day.

While erythropoiesis was normal, platelet counts were decreased up to 120,000/mm³ on the 18th day and it recovered since the 23rd day.

Sternal bone marrow showed moderate hypoplasia with relative increase of plasma cells and reticulum cells at the 9th day. Sternal bone marrow was almost normalized at the 27th day while the signs of regeneration in hematopoiesis remained until 62 days after the initial exposure.

It is a noticeable thing in this case that the bone marrow aspirate from iliac crest showed more severe hypoplastic changes than sternal bone marrow on the 17th day. Furthermore, on the 62nd day the bone marrow from iliac crest still remained hypoplastic whereas the marrow from sternum showed hyperplastic figure after recovery.

The other case, K.J. (23 Yr.), who was delayed to admission and suffered from the erythema and blisters of right hand caused by 192Ir source, showed only leukopenia (3,300/mm³) on the 24th day. Thereafter W.B.C. count increased with fluctuating waves and reached a normal value on the 56th day. The changes of bone marrow also showed the hypoplasia on the 24th day and almost normalized on the 62nd day after initial exposure.

**DISCUSSION**

Recently the same type of radiation accident by 192Ir source was reported. In that case, only one person among 6 workers showed the gamma-rays burns and the hypoplasia of the bone marrow in the iliac crest on irradiated side. The changes of blood were not observed. Our reported accident involved three cases of gamma-rays burns, 4 cases with slight or moderate and one case with severe hematological...
disorders. Our cases were irradiated during several days and hospitalized more than a week after the initial exposure. In this circumstance, the exact evaluation of the radiation doses received presented difficult problems. Following the reconstruction experiments based on the behaviors of six persons, the physical estimation was performed. On the other hand, the absorbed doses of each person were estimated by cytogenetic analysis of peripheral lymphocytes.

It was shown that the average total body absorbed doses (equivalent to 60Co gamma-rays) were 124 rad for S. H., 40 rad for Y. S., 26 rad for K. J., 12.2 rad for M. K., 10.9 rad for T. S. and 9.8 rad for M. I. respectively.

These values by cytogenetic studies were quite well corresponded to those by the physical estimation. However, about a case of S. H., who showed severe hematological disorders, the changes of hematopoiesis were impressed of more severe than those caused by 124 rad gamma-rays irradiation.

The utilization of measured hematologic changes as a direct indicator of the severity of radiation injury provides meaningful information for diagnosis and prognostic evaluation in individual cases.

According to Wald, the exposure dose of S. H. calculated from the fall of lymphocyte count is between 200 rad to 500 rad.

Relating to neutrophil count in blood, the severe depression in 3 to 5 weeks, such as S. H. case, means 200-500 rad as the exposure dose.

Moreover, the severe depression of platelets in 3-5 weeks indicated 200-500 rad. The fall of reticulocyte counts also means the similar exposure dose.

Furthermore, hematologic changes can be described in terms of prognostic categories based on the possible outcome of the acute radiation syndrome. The five categories suggested by Thoma and Wald are quite well agree to that of our S. H. case. (Fig. 4) Summarizing on these data and related papers, the exposure dose of hematopoietic organs in S. H. case is estimated 200-400 rad. The rea...
sons of the difference between the hematological effects and the exposed dose estimated from cytogenetics will be ascribed to the non-uniform exposure of S.H. case.

Supposedly, the exposure dose of the trunk including most of active bone marrow and hematopoietic stem-cell will be much greater than that of extremities. This concept is supported by the value of 500 rad as the maximum absorbed dose one middle line in trunk calculated by the physical estimation.\(^5\)

Moreover, the difference between radio-sensitivity of peripheral lymphocytes reacted phytohemagglutinin in the method of the present cytogenetic dosimetry and that of hematopoietic stem-cell should be clarified more exactly in future.

S. H. case was treated with minimum dose of antibiotics without any modification such as blood transfusion or platelets transfusion.

Moreover, any signs of bacterial and viral infection were not observed except the erythema and blisters in hands which were contacted \(^{192}\text{Ir}\) source. Therefore, in this case, the hematopoietic injuries by gamma-rays irradiation in human being can be purely analysed without any other modification. An early lymphopenia developed and persisted. All cell components of hematopoiesis decreased rapidly and showed pancytopenia during the 3rd and 7th week after the initial exposure. In this period, it was considered as the most important for clinical treatments to know whether the degenerative changes of hematopoiesis still develop or not and to detect the distinct signs of the initiating recovery process. According to the recent concepts of hematopoietic injuries by ionizing irradiation, the depopulation and repopulation of the hematopoietic multipotential stem-cells should play the essential role in the mechanism after irradiation.

Therefore, if we can be convinced of the initiation of the recovery process in any hematopoietic cell-lines, the further potential replacement therapies such as blood transfusion or bone marrow transplantation which might cause the severe side effects on the patients can be avoidable.

In S. H. case, during this critical period, the increase of reticulocyte began since the 25th day and increase of platelets and leukocytes in blood was also observed since the 30th day after the initial exposure.

However, the changes of these cell counts were too small to ensure the true initiation of hematopoiesis sufficiently. The most useful method for evaluating the developing recovery was thrombelastograph. The values of m. a. (Maximum Amplitude) of thrombelastogram decreased (34.5 mm) on the 25th day but the significant increase of m. a. was observed since the 32nd days (43.0 on the 32nd, 48.0 mm on the 34th day).

Between the 30th and 34th day, whereas the values of leukocytes and platelets were the lowest, we were convinced of the initiation of hematopoietic recovery by the data of thrombelastograph. Thereafter the hematopoietic recovery was rapid in aseptic conditions.

Thrombelastograph is one of the most useful tool to know the prognosis and to
decide the treatments in this crucial pancytopenic period after radiation exposure as described on the paper about Mole accident.\textsuperscript{12)}

About the other cases of this accident, the fall of total lymphocyte counts in each person was very well corresponded to the exposed doses estimated from cytogenetic analysis. (Fig. 3) Moreover, even under very low level of exposure (M. K. and T. S.), the careful hematological examination can detect the effects of the irradiation such as slight leukopenia and signs of bone marrow regeneration.

For a diagnostic and prognostic tool, studies on the changes of hematopoiesis is one of the simplest and most useful indices of radiation effects.

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