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Abstract

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PRELEUKEMIA: HEMATOLOGICAL DISORDERS PRIOR TO ONSET OF LEUKEMIA

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Abstract: Published data on Japanese leukemia patients with a preleukemic hematological disorder were assessed. The reexamined cases were from the "Japona Centra Revuo Medicina" reported during the period from 1952 to 1971. Among preleukemic hematological disorders, hypoplastic anemia was the most frequently reported (41 of 62 cases). These "hypoplastic preleukemia" patients were rather elderly and terminated mostly in atypical myelocytic leukemia. The chief hematological feature of the hypoplastic preleukemia cases was the coexistence of a relative erythroid hyperplasia and a slight increase of myeloblasts in the bone marrow that was unusual in hypoplastic anemia. The presence of pancytopenia and hypocellular marrow with a relative erythroid hyperplasia combined with a slight increase of myeloblasts probably indicates hypoplastic preleukemia that terminates later in acute leukemia.

The terms "preleukemia" and "preleukemic stage" have been applied to hematological disorders prior to the onset of leukemia. Experimentally, hypoplastic anemia-like hematological findings, such as pancytopenia and hypocellular marrow, have been observed frequently in murine leukemias induced by chemicals, irradiation and viruses (1, 2, 3). Since the report of Block, Jacobson and Bethard (4) in 1953, many reports on this subject have been published. Hypoplastic anemia, sideroblastic anemia and a few other hematological disorders have been confused with the preleukemic stage (5, 6, 7, 8, 9, 10, 11, 12, 13, 14).

In Japan, clinical investigations of the preleukemic stage have been conducted systematically with atomic bomb survivors (15, 16). In many cases, no leukemogenetic agents, such as irradiation or chemicals, have been identified. What sorts of hematological changes are present most frequently in these cases? Are there hematological and clinical characteristics in leukemia with a preleukemic stage? The present paper examines the types, incidences and some selected clinical data on leukemia cases with a preleukemic stage in the Japanese literature.

MATERIALS AND METHODS

A total of 62 cases of leukemia with a preleukemic stage were collected from the "Japona Centra Revuo Medicina." These cases were reported in Japan during the period from 1952 to 1971. The reports were collected under the title of preleukemic stage, abnormal hematological changes prior to the development of leukemia (17). Cases of atomic bomb casualties and congenital hematological diseases were excluded. Clinical and hematological studies were performed by the reporting investigators. They were particularly detailed in cases of hypoplastic preleukemic stage. The term "hypoplastic preleukemic stage" was applied to cases of hypoplastic anemia which terminated later in leukemia.

RESULTS

Preleukemic hematological disorders and their incidences

Various preleukemic hematogical disorders were reported (Table 1). The clinical diagnosis of hypoplastic anemia was most frequent (41 of 62 cases, 66.1%). Preleukemic reports of erythropoiesis disturbances including sideroblastic anemia and pernicious anemia were present in eight cases, and myeloproliferative disorders, such as myelofibrosis and polycythemia vera, were found in six cases.

TABLE 1. REPORTED CASES OF LEUKEMIA WITH A PRELEUKEMIC HEMATOLOGICAL DISORDER IN JAPAN FROM 1952-1971

	Number
Hypoplastic anemia	41
Sideroblastic anemia	1
Hyperchromic megaloblastic anemia	2
Refractory normoblastic anemia	1
Achrestic anemia	1
Pernicious anemia	3
Polycythemia vera	2
Polycythemia-Myelofibrosis	1
Myelofibrosis	3
Banti's syndrome	2
Others	5
Total	62

Sex and age distributions of cases with a preleukemic stage

The male-to-female ratio in 58 cases (4 unknown cases excluded) was 36 : 22. The age distribution of the sample is shown in Fig. 1.

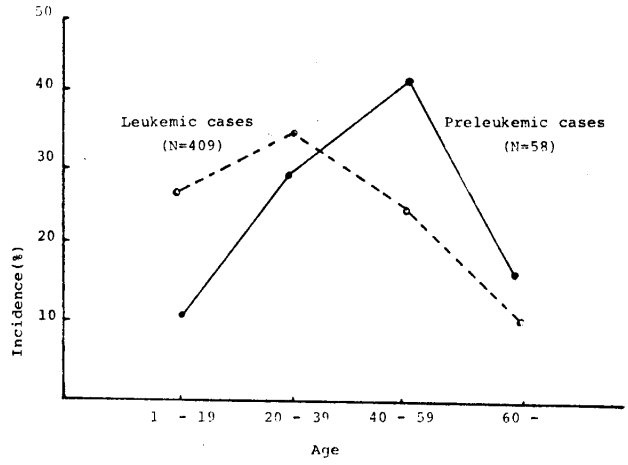

Fig. 1. Aged distribution of preleukemic cases. The leukemic sample was from our clinic.

Leukemia cases from our clinic were used as controls. The preleukemic stage tended to be more frequently in cases of the fourth or fifth decade of life. In 39 cases with a hypoplastic preleukemic stage (2 unknown cases excluded), the male-to-female ratio was 25 : 14. Of 41 cases, 22 cases (53.6%) were above the fourth decade of life.

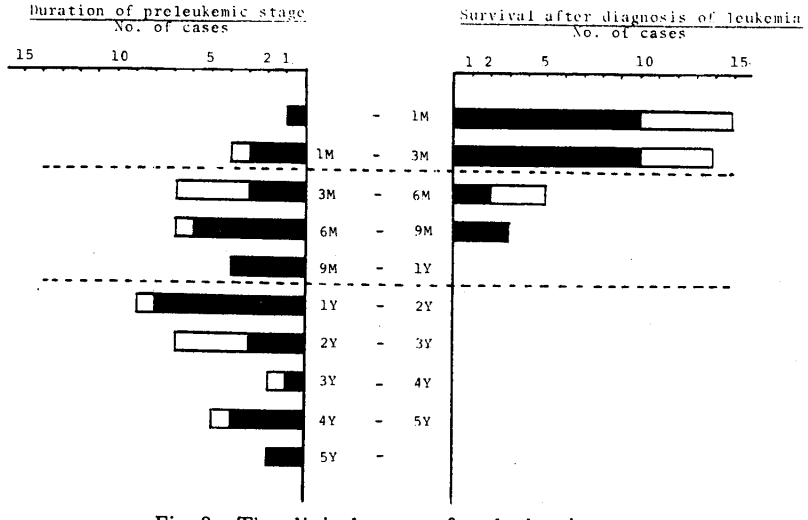

Fig. 2. The clinical course of preleukemic cases.
■, Hypoplastic preleukemic cases
□, Other preleukemic cases
M, month; Y, year

Clinical course of leukemia with a preleukemic stage

The duration of the preleukemic stage and survival time after the establishment of leukemia diagnosis are summarized in Fig. 2. The duration and survival time were too variable for definitive conclusions. It can be said that the preleukemic hematological changes tended to be short once the diagnosis of leukemia was established. This tendency was also present in cases with a hypoplastic preleukemic stage.

Types of leukemia with a preleukemic stage

The types of leukemia in the 57 cases (5 unknown cases excluded) with a preleukemic stage are listed in Table 2. Fifty-one cases were diagnosed as acute leukemia (31 acute myelocytic leukemia, 7 monocytic leukemia, 5 acute lymphocytic leukemia, 2 erythroleukemia and 6 unknown types). Thirty-seven of these 51 cases (72.6%) passed through a hypoplastic preleukemic stage. This suggests a close relationship between acute leukemia and a hypoplastic preleukemic stage.

TABLE 2. TYPES OF LEUKEMIA WITH HYPOPLASTIC PRELEUKEMIC STAGE

Types of leukemia	Total cases	Cases with hypoplastic preleukemic stage
Acute leukemia		
Acute myelocytic leukemia	31	22
Monocytic leukemia	7	5
Erythroleukemia	2	2
Acute lymphocytic leukemia	5	3
Unknown	6	5
Chronic leukemia		
Chronic myelocytic leukemia	6	0
Chronic lymphocytic leukemia	0	0
Unknown	5	4

Hematological characteristics of cases with hypoplastic preleukemic stage

All 41 cases with a hypoplastic preleukemic stage underwent some treatment for hypoplastic anemia. Some authors indicated reservations on the diagnosis of hypoplastic anemia. These cases had evidence of monocytosis, reticulocytosis and the appearance of erythroblasts, immature cells and undifferentiated cells in peripheral blood and a relative erythroid hyperplasia, a slight increase of myeloblasts, a shift to the left of the granulocyte series and the appearance of undifferentiated cells in the bone marrow. The incidences of these hematological findings in 16 cases in which detailed data were available are listed in Table 3. Three major features were present in high frequency: the appearance of erythroblasts in peripheral blood (68.8%),

the slight increase of myeloblasts (68.8%) and a relative erythroid hyperplasia in the bone marrow (81.3%). Two of these features, a relative erythroid hyperplasia and a slight increase of myeloblasts, were present simultaneously in 10 of 16 cases (62.5%). These 16 cases terminated in acute leukemia. At the time of leukemia diagnosis about 60% of cases were aleukemic-hypocellular, and blasts were found at low percentage (less than 10% in the peripheral blood) in 7 of 16 cases (43.7%) (Table 4).

TABLE 3. ATYPICAL HEMATOLOGICAL FINDINGS IN 16 CASES OF CLINICALLY DIAGNOSED LEUKEMIA WITH A HYPOPLASTIC PRELEUKEMIC STAGE

Hematological findings	No. of cases
Peripheral blood	
Monocytosis	1
Reticulocytosis	6
Plasmocyte (+)	1
Immature cell of granulocyte series (+)	2
Erythroblast (+)	11
Undifferentiated cell (+)	3
Bone marrow	
Relative erythroid hyperplasia	13
Slight increase of myeloblast	11
Left shift of granulocyte series	3
Monocytosis	1
Plasmocytosis	1
Undifferentiated cell (+)	4

TABLE 4. HEMATOLOGICAL FINDINGS AT DIAGNOSIS OF LEUKEMIA IN 16 CASES WITH A HYPOPLASTIC PRELEUKEMIC STAGE

Hematological findings	No. of cases
Peripheral blood	
Normal or decreased WBC	10
Low percentage of blasts (below 10%)	7
Bone marrow	
Decreased NCC (below 70,000)	8/13 cases
Low percentage of blasts (below 20%)	4/14 cases

DISCUSSION

This investigation showed that the hypoplastic preleukemic stage was the most frequently reported preleukemic hematological disorder in Japan during the period from 1951 to 1971. It is uncertain whether a hypoplastic or hypocellular marrow was present before the onset of leukemia. Hiraki and Irino (1) and Soda (2) reported that the hypoplastic marrow preceded an abrupt increase of leukemic cells in 20-methyl-cholanthrene-induced and

radiation-induced murine leukemia. Furthermore, they reported hypoplasia of the bone marrow at the preleukemic stage in tissue cultures of bone marrow cells. We have also observed this phenomenon at the preleukemic stage in BALB/c mice inoculated with Rauscher leukemia virus. From these data, we can postulate that the hypoplastic anemia-like hematological findings precede the onset of human leukemia.

It may be important clinically to differentiate the hypoplastic preleukemic stage from the so-called hypoplastic anemia in patients with pancytopenia and hypoplastic marrow. In hematological examinations of 86 cases with idiopathic hypoplastic anemia admitted to our clinic in the past 20 years, a number of atypical hematological findings were determined. These atypical findings in hypoplastic anemia corresponded to the unusual hematological findings detected in the 41 reported cases of hypoplastic preleukemic stage. Among these atypical findings, the coexistence of a relative erythroid hyperplasia and a slight increase of myeloblasts in the bone marrow was observed in a high percentage of hypoplastic preleukemic cases. This coexistence was seldom found in hypoplastic anemia (18). It may, therefore, be a useful clue in the diagnosis of the hypoplastic preleukemic stage.

It is interesting to determine whether all types of leukemia have a preleukemic stage. Acute leukemia was found in 51 of 57 cases with a preleukemic stage. Thirty-seven of these 51 cases (72.6%) passed through the hypoplastic preleukemic stage. The hematological findings tended to be mostly atypical at the time of leukemia diagnosis. In our clinic we have examined 22 cases of acute leukemia with hypoplastic marrow. They were characterized by poor clinical and physical signs (such as fever, petechiae and hepatosplenomegaly), slow progress, aleukemic with few or no leukemic cells in the peripheral blood and hypoplastic marrows. Some of these patients were observed under the clinical diagnosis of hypoplastic anemia for a relatively long time until leukemia was diagnosed. From these data, it may be suggested that a close relationship exists between the hypoplastic preleukemic stage and acute, mostly atypical, leukemia. Sex and age distributions of hypoplastic preleukemic cases may give some clues, although the data are variable except for the elderly who are more frequently affected. In the elderly, the bone marrow tended toward hypofunction (19), and in elderly patients with leukemia, the clinical and hematological findings tended to be atypical (20). These points were helpful in the diagnosis of the hypoplastic preleukemic stage as the initial step of leukemia in elderly patients.

The present survey found that a hypoplastic preleukemic stage was frequent among patients that terminated in acute myelocytic leukemia. However, the following points are uncertain: (a) whether normal hematopoietic cells

become malignant in the course of so-called hypoplastic anemia or (b) whether the hypoplastic preleukemic stage is latent leukemia. The authors favor the second hypothesis. Aplastic or hypoplastic anemia was reported by Ehrlich (21) in 1888. Since then, this term has been loosely applied to cases with pancytopenia and hypoplastic marrows. Other hematological diseases may be excluded if more rigid examinations were performed. Our investigation suggests that the hypoplastic preleukemic stage is characterized by the coexistence of a relative erythroid hyperplasia and a slight increase of myeloblasts in the bone marrow, which is seldom found in so-called hypoplastic anemia. Hypoplastic preleukemia should be suspected in the presence of pancytopenia and hypocellular or hypoplastic marrow with a relative erythroid hyperplasia and a slight increase of myeloblasts.

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