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Acute Non-lymphocytic Leukemia Is Not a Major Type of Childhood Leukemia in Japan

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Abstract—*The distribution of acute leukemia according to type was examined in Japanese children by three surveys: (1) a review of bone marrow slides of 81 cases diagnosed as acute myelogenous leukemia between 1964 and 1976; (2) a prospective study of 97 cases observed since 1977, and (3) a study of 8108 cases registered with the Children's Cancer Registry of Japan from 1969 to 1984. The results indicate that the ratio of acute lymphocytic leukemia to non-lymphocytic leukemia in Japan is not different from that in other countries.*

INTRODUCTION

EPIDEMIOLOGICAL studies of cancer have often provided important clues regarding cancer etiology. In order for this type of study to be successful, an accurate demographic description is essential. A recent article dealing with the epidemiology of leukemia contained a description concerning the distribution of various types of leukemia in Japan which was, in fact, based upon incorrect information [1]. This prompted us to translate the old data for publication in the English literature. A part of the data has been published in Japanese in the past [2].

MATERIALS AND METHODS

Review of bone marrow slides at the time of diagnosis (retrospective study)

Bone marrow slides of 81 cases (old cases) which had been observed at the Department of Pediatrics of the University of Tokyo Hospital between 1964 and 1976, and had been diagnosed as either acute myeloblastic leukemia (AMbL), acute promyelocytic leukemia (APL), acute myelomonocytic leukemia (AMMoL) or acute monocytic leukemia (AMoL), were reviewed in 1978. Peroxidase reaction products had faded away in the majority cases. Data found on the medical charts, therefore, were used for the evaluation of peroxidase positivity. As far as original stains are concerned, only May–Grünwald–Giemsa stained smears were used for this review. In none of the cases during this period was the periodic acid–Schiff reaction used.

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Prospective study

All cases (new cases) of leukemia observed at the Department of Pediatrics of the University of Tokyo Hospital or at affiliated hospitals since 1977 were typed according to the criteria of the French–American–British Group [3]. Bone marrow or peripheral blood samples were stained with May–Grünwald–Giemsa. Samples were also cytochemically stained for peroxidase, α-naphthyl butyrate esterase and naphthol AS-D chloroacetate esterase. T-cell markers were evaluated by rosette formation with sheep erythrocytes or with several types of anti-T-cell monoclonal antibodies. B-cell markers were evaluated by EAC rosette formation or by detection of surface immunoglobulins and, in recent years, by reaction with various kinds of anti-B-cell monoclonal antibodies, including anti-cALLA.

Data from the Children's Cancer Registry of Japan

The Children's Cancer Registry of Japan was established in 1969 under the sponsorship of the Children's Cancer Association of Japan with the expectation of registering all cases of children's cancer. All cases of leukemia registered in this nationwide registry since 1969 were classified on the basis of descriptions appearing on the registration forms.

RESULTS

Retrospective study

Sixty-five of the 81 slides examined were of evaluable quality. The distribution of the reclassified types of leukemia is shown in Table 1. Twenty-eight of 33 cases which were originally classified

Table 1. Reclassification of acute leukemia of children which had originally been classified as acute myelogenous leukemia

Original classification	New classification*									NA	NE	R
	L1	L2	L3	M1	M2	M3	M4	M5	M6			
AMbL	13	15	0	4	1	0	0	0	0	5	3	3
APL	0	1	0	1	13	2	5	2	0	3	1	0
AMMoL	0	0	0	0	0	0	1	0	0	0	0	0
AMoL	0	0	0	0	0	0	0	7	0	1	0	0
Total	13	16	0	5	14	2	6	9	0	9	4	3
ANLL†	—	—	—	1	10	4	2	2	0	—	—	—

*Nomenclature according to French–American–British classification.
†Non-lymphocytic leukemia observed since 1977.
AMbL: acute myeloblastic leukemia; APL: acute promyelocytic leukemia; AMMoL: acute myelomonocytic leukemia; AMoL: acute monocytic leukemia; NA: not available; NE: not evaluable; R: referred after relapse.

as AMbL were reclassified as acute lymphocytic leukemia (ALL). Information regarding peroxidase reactivity was available for 17 of the 33 cases with only three of these being positive. Other major changes of classification were observed in cases of original APL, that is, 13 of 24 cases of APL were reclassified as FAB M2. All of these 13 cases lacked the clinical pictures of disseminated intravascular coagulation. Only two cases were compatible with FAB M3. One case of original APL tested negative for peroxidase reaction, the sole reason for its classification as APL being the presence of a few coarse granules in the blast cells.

During this period 78 cases were diagnosed as ALL or 'leukoblastic' leukemia, the nomenclature for a special type of ALL which was sometimes classified as 'unclassified leukemia' (see below for nomenclature). In total, 107 cases (74.8%) were classified as ALL.

Prospective study

Since 1977, 97 cases of leukemia have been observed. Of these, 78 cases (80.4%) were ALL and 19 cases (19.6%) were acute non-lymphocytic leukemia (ANLL) (Table 2). The subtype distribution of ANLL is given in Table 1.

Data from the Children's Cancer Registry of Japan

From 1969 to 1984, 8108 cases of acute leukemia were registered in Japan. The type distribution of these cases is shown in the figure. A progressive increase in the proportion of ALL cases is apparent. Whereas 152 of 349 classifiable cases (43.6%) were ALL in 1969, 400 of 497 (80.5%) were ALL in 1984. Furthermore, a concomitant decrease in the proportion of unclassified leukemia cases is noted. The majority of unclassified leukemia cases during early years of this study period tended to be 'leukoblastic' leukemia.

DISCUSSION

Several studies dealing with descriptive epidemiology, including a very recent review, have contained incorrect data concerning the type distribution of acute leukemia in Japanese children [1, 4, 5]. These studies indicated the predominance

Table 2. Comparison of ALL/ANLL ratios between old and new classification systems

	1964–1977							
	Old		New*		1977–		Total†	
ANLL	81	(50.9)	36	(25.2)	19	(19.6)	55	(22.9)
ALL or Lbl	78	(49.1)	107	(74.8)	78	(80.4)	185	(77.1)
Total	159		143		97		240	
ALL/ANLL	0.96		3.0		4.11		3.36	

*Cases of NA, NE and R in Table 1 are omitted.
†New plus 1977–.
ALL: acute lymphocytic leukemia; LbL: 'leukoblastic' leukemia; ANLL: acute non-lymphocytic leukemia; percentages in parentheses.

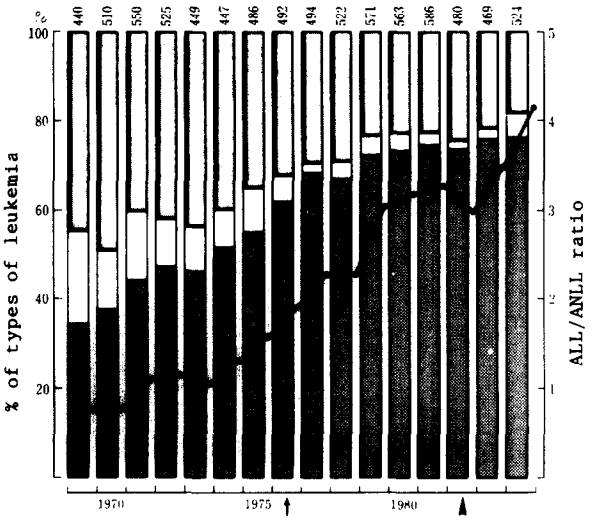

Fig. 1. Type distribution trend of acute leukemia in Japanese children observed in the Children's Cancer Registry of Japan. The upper shaded portions of bars indicate the percentages of acute non-lymphocytic leukemia and the lower shaded portions indicate the percentages of acute lymphocytic leukemia. The white areas in the middle represent the percentages of unclassified leukemia. The numbers at the top of each of the bars indicate the total number of registered cases of acute leukemia in each year. The line indicates ALL/ANLL ratios. The arrow and arrow head indicate the year in which articles dealing with surface marker analysis of leukemic cells first appeared and the year in which articles in which monoclonal antibodies were used to analyze surface markers of leukemic cells first appeared, respectively, in meetings of the Japanese Society of Clinical Hematology.

of acute myelogenous leukemia (AML) over acute lymphocytic leukemia (ALL) among Japanese children as well as the greater incidence of AML than ALL for all age groups in Japan.

The present study shows rather rapid changes in the type distribution of cases registered in the Registry of Children's Cancer. Although similar changes in type distribution have been reported in several other countries [6, 7], the changes seen in the Japanese registry data are more likely a reflection of the unique situation in Japan.

The main reason for these changes is the employment of improved classification techniques. The first appearances of articles in meetings of the Japanese Society of Clinical Hematology dealing with surface marker analysis of leukemic cells as well as the employment of monoclonal antibodies for surface marker analysis are apparently associated with these changes.

Some time ago much effort was made at the Department of Pediatrics of the University of Tokyo Hospital to further classify peroxidase-negative acute leukemia, with supravital staining methods [8] being found to be suitable for this purpose. As a result, some cases of peroxidase-negative leukemia were classified as peroxidase-negative myeloblastic leukemia and others as 'leukoblastic' leukemia [9, 10]. Only a minority of cases, however, were classified as ALL. The uniqueness of this classification system is reflected in the fact that a case of leukemia whose blast cells formed rosettes with sheep erythrocytes was classified as 'leukoblastic' leukemia.

In the retrospective study presented here, which ignored the results of supravital staining, the majority of peroxidase-negative myeloblastic leukemia cases were reclassified as ALL. The newly formed type distribution of old cases is quite similar to that of new cases in Japan and in other countries [11, 12].

In the past, the majority of Japanese hematologists believed in this misconception since they used this classification system. Therefore, the type distribution observed in the nationwide registration in the past is more likely a reflection of the classification system rather than the biological nature of acute leukemia in Japanese children.

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