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A STUDY OF LEUKEMIC CELL INFILTRATION IN THE TESTIS AND OVARY

BY

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ABSTRACT

The behavior of leukemic cell infiltration in the testis or ovary was examined on 99 autopsy cases of various leukemia, which were performed in the Department of Pathology, Tokyo Medical and Dental University, from 1964 to 1975.

The incidence of leukemic cell infiltration was 48.5% in the testis and 58.1% in the ovary. The frequency of leukemic cell infiltration in the testis or ovary itself showed no significant increase in recent years, although median survival time became longer by a more aggressive combination chemotherapy. These findings show that the testis and ovary are essentially a preferred site of leukemic cell infiltration. Especially in acute monocytic leukemia, leukemic cell infiltration was revealed in all cases.

In addition, short discussions were made on the role of sex hormones in the infiltration, proliferation, and persistence of leukemic cells of each type of leukemia in the testis or ovary.

INTRODUCTION

In recent years, leukemia is treated by various combination chemotherapy from the development of many antileukemic drugs and the concept of the so-called "total cell kill"[1]. Reports of long-term survivor are increasing and median survival time is now longer than ever. These facts have induced changes in direct cause of death in leukemia, namely, decrease of significant hemorrhage, and increased infection of gram-negative bacillus, fungus,, and protozoa such as pneumocystic carinii and toxoplasma gondii, etc.[2-3].

In addition, it is remarked that leukemic cell infiltration in the extramedullary organs, especially in the central nervous system, testis, ovary, and mammary gland, persists during hematological remission[4-8]. Concerning leukemic cell infiltration in the meninges, *i.e.*, the so-called meningeal leukemia, many investigations have been performed clinically and pathologically, and it is thought that meningeal leukemia is principally induced by the existence of a "blood-brain barrier" which antileukemic drugs have difficulty in penetrating[9-12]. On the other hand, there are only a few studies to date on leukemic cell infiltration in the testis or ovary[4,5,7].

We examined statistically the behavior of leukemic cell infiltration in the testis or ovary on 99 autopsy cases, and its results are reported in this paper with some discussions.

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Table 1. Incidence of leukemic cell infiltration in the testis and ovary

	AL	AML	AProL	CML	AMoL	ALL	CLL	EL	Total
Testis	9/14	9/24	0/9	1/5	7/7	5/5	1/1	1/3	33/68
	64.3%	37.5%	0%	20.0%	100%	100%	100%	33.3%	48.5%
Ovary	3/5	9/13	1/3	0/3	2/2	3/4		0/1	18/31
	60.0%	69.2%	33.3%	0%	100%	75.0%		0%	58.1%

Key to Abbreviation (Table 1-3 and Fig. 2-11):

AL: Acute leukemia
AML: Acute myelogenous leukemia
AProl: Acute promylocytic leukemia
CML: Chronic myelogenous leukemia
AMol: Acute monocytic leukemia
ALL: Acute lymphatic leukemia
CLL: Chronic lymphatic leukemia
EL: Erythroleukemia
H.E.: Hematoxylin-Eosin stain

Materials and Methods

Ninety-nine autopsy cases of various leukemia were studied for the present investigation, which were performed in the Department of Pathology, Tokyo Medical and Dental University, during 1964 to 1975. The testis or ovary was stained with Hematoxylin-Eosin and/or Giemsa from paraffin sections. Leukemic cell infiltration was graded as negative(−), slight(+), moderate (++), and marked (+++) (Figs. 2–7). The clinical data such as hematological remission, median survival time, etc. were carefully examined from the protocols.

Results

The incidence of leukemic cell infiltration was 33 cases among 68 autopsies (48.5%) in the testis, and 18 cases among 31 autopsies (58.1%) in the ovary (Table 1). Concerning the type of leukemia, leukemic cell infiltration in the testis or ovary was seen in all cases of acute monocytic leukemia and almost all of acute lymphatic leukemia, while the frequency of leukemic cell infiltration was relatively low in acute promyelocytic leukemia, chronic myelogenous leukemia, and erythroleukemia. In acute leukemia and acute myelogenous leukemia, the frequency was of moderate degree. It is not possible to discuss the signification of this frequency, because there was only one case of chronic lymphatic leukemia.

In age distribution, incidence of leukemic cell infiltration in the testic was high in 0–19 year age groups, and relatively low in the other age groups, because acute lymphatic leukemia among various leukemia was high in the 0–19 year age groups. On the other hand, leukemic cell infiltration in the ovary was revealed only in acute lymphatic leukemia in the 0–9 year age group, the incidence of ovarian infiltration in other leukemic types was higher in 10–59 year age groups, although there were only a few cases in 20–29 and 50–59 year age groups (Table 2).

The grade of leukemic cell infiltration in the testis tended to be severer in the 0–39 year age groups than in older age groups. In the ovary, moderate to marked degree of leukemic cell infiltration was also observed in the 10–49 year age groups, although this was only in slight degree in 0–9 and 50–59 year age groups (Fig. 1). Moreover, in acute lymphatic leukemia, leukemic cell infiltration was generally moderate to marked degree in the testis while slight in the ovary.

Leukemic cell infiltration in the testis was 41.7% in the 1964 to 1969 series, and 56.3% in the 1970 to 1975 series that more aggressive combination chemotherapy for

Table 2. Age distribution of leukemic cell infiltration in the testis and ovary

Age	(yr)	10		20	30	40	50	60	70	
AL	Testis	3/5	3/3	1/1	1/4	1/1				
	Ovary	0/2	1/1		1/1	1/1				
AML	Testis		0/1	2/6	2/5	0/2	4/7	1/2	0/1	
	Ovary	0/1	2/2	1/1	2/3	3/4	1/1	0/1		
AProL	Testis			0/3	0/1	0/3	0/1	0/1		
	Ovary				1/2			0/1		
CML	Testis			1/4		0/1				
	Ovary		0/1		0/1	0/1				
AMoL	Testis		2/2	1/1	2/2	1/1	1/1			
	Ovary				1/1		1/1			
ALL	Testis	2/2	3/3							
	Ovary	2/3	1/1							
CLL	Testis						1/1			
	Ovary									
EL	Testis			0/1	1/1			0/1		
	Ovary	0/1								
Total	Testis	5/7	8/9	5/16	6/13	2/8	6/10	1/4	0/1	
		71.4%	88.9%	31.3%	46.2%	25.0%	60.0%	25.0%	0%	
	Ovary	2/7	4/5	1/1	5/8	4/6	2/2	0/2		
		28.6%	80.0%	100%	62.5%	66.7%	100%	0%		

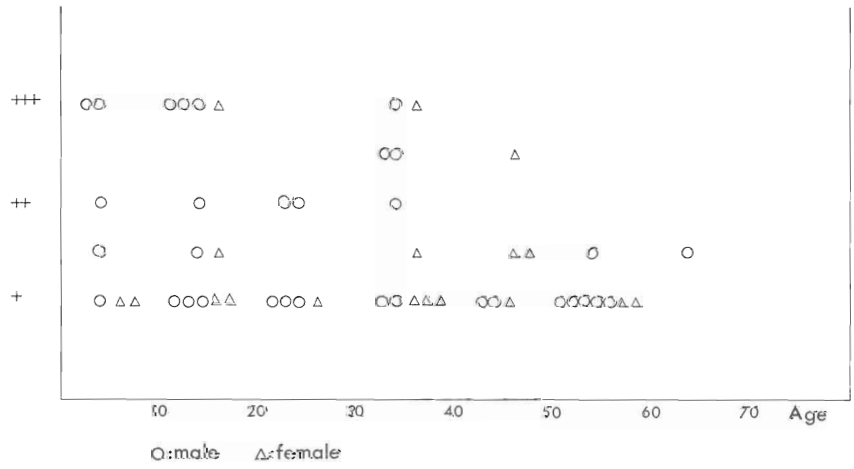

Fig. 1. Degree of leukemic cell infiltration in the testis and ovary

"total cell kill" was performed and median survival time became longer. Ovarian infiltration was 66.7% in the 1964 to 1969 series and 46.2% in the 1970 to 1975 series. These analyses also showed the same results in each type of leukemia (Table 3). By the way, leukemic cell infiltration was revealed in the testis of 12 cases among 13 autopsies and in the ovary of all cases among seven autopsies, which were not treated by aggressive chemotherapy in the 1954 to 1963 series.

Moreover, there were three cases (acute lymphatic leukemia in 17-year-old male; acute leukemia in 28-year-old male and acute leukemia in 32-year-old female) in

Table 3. Incidence of leukemic cell infiltration and median survival time (1964–1969 and 1970–1975)

		1964–1969	1970–1975
AL	Testis	3/5	6/9
	Ovary	1/2	2/3
	Median survival time	7.0 mo.	8.0 mo.
AML	Testis	6/15	3/9
	Ovary	7/9	2/4
	Median survival time	4.5 mo.	8.0 mo.
AProL	Testis	0/5	0/4
	Ovary	1/2	0/1
	Median survival time	20 days	21 days
CML	Testis	0/3	1/2
	Ovary	0/1	0/2
	Median survival time	23.5 mo.	49.5 mo.
AMoL	Testis	2/2	5/5
	Ovary	1/1	1/1
	Median survival time	3.5 mo.	4.5 mo.
ALL	Testis	2/2	3/3
	Ovary	2/3	1/1
	Median survival time	6.5 mo.	14.3 mo.
CLL	Testis	1/1	—
	Ovary	—	—
	Median survival time	—	—
EL	Testis	1/3	—
	Ovary	—	0/1
	Median survival time	—	—
Total	Testis	15/36 (41.7%)	18/32 (56.3%)
	Ovary	12/18 (66.7%)	6/13 (46.2%)

the 1970 to 1975 series, in which leukemic cell infiltration were found only in the testis, ovary, meninges, and peritoneum during bone marrow remission (Fig. 8–11).

Discussion

At autopsy, the incidence of leukemic cell infiltration was 48.5% in the testis and 58.1% in the ovary. This finding indicates that the testis and ovary are generally a preferred site of leukemic cell infiltration, although its frequency varies with each type of leukemia. Especially, in all cases of acute monocytic leukemia, leukemic cell infiltration was found in the testis or ovary. It is thought that this result also shows a characteristic of acute monocytic leukemia, in addition to the report[13] that the frequency of leukemic cell infiltration in the skin, connective tissue, alimentary tract, and perirectal area is higher in acute monocytic leukemia than in other leukemic types.

Leukemic cell infiltration in the testis during bone marrow remission has been reported, especially in the cases of children in recent years[4,7], and it is speculated[4] that the testis is a "sanctuary organ", with the existence of a "blood-gonad barrier" similar to the "blood-brain barrier", which antileukemic drugs have difficulty in penetrating. On the other hand, it is reported that estrogen has a leukemogenic effect, while leukemogenesis is repressed by androgen in experimental studies with mice[14]. Grabnick and Dittmar[5] reported

that massive breast and ovarian involvement of leukemia during hematological remission was observed in acute myelogenous leukemia of a 13-year-old girl who was attacked with the disease two weeks after her menarche. They raise the question of whether the onset of menarche with the increased estrogen level may have induced the leukemic process or accelerated its growth, or influenced the massive breast and ovarian involvement which are the target organs of estrogens.

In our study, leukemic cell infiltration in the testis or ovary was seen in almost all cases which were not treated by aggressive chemotherapy in the 1954 to 1963 series. Moreover, the incidence of leukemic cell infiltration in the testis or ovary had no significant difference between 1964 to 1969 series and 1970 to 1975 one. In other words, leukemic cell infiltration in the testis or ovary itself has not increased in recent years, although median survival time is certainly longer by the use of a more aggressive combination chemotherapy of antileukemic agents for "total cell kill". These facts show also that the testis or ovary is essentially a preferred site of leukemic cell infiltration as mentioned above.

In addition, the incidence of leukemic cell infiltration in the ovary was higher and its degree was severer in the age groups when secretion of estrogen increases than in other age groups. The incidence of leukemic cell infiltration in the testis or ovary varied with each leukemic type, *i.e.*, very high frequency in acute monocytic leukemia and acute lymphatic leukemia, while relatively low in acute promyelocytic leukemia, chronic myelogenous leukemia, and erythroleukemia. These findings pose the question that sex hormones may take part in the difference of affinity of leukemic cell infiltration and its proliferation in the testis or ovary of each type of leukemia, as Gralnick and Dittmar[5] speculated.

Moreover, there were three cases in our 1970 to 1975 series, in which leukemic cell infiltrated only in the testis, ovary, meninges, and peritoneum during hematological remission. Including these cases, leukemic cell infiltration is seen in the interstitial tissue of the testis, in which the so-called "blood-gonad barrier" does not play a part. Namely, it seems that the persistence of leukemic cell infiltration in these extramedullary organs during hematological remission cannot be attributed only to the existence of the so-called "blood-gonad barrier". These findings may also suggest that sex hormones influence the persistence and proliferation of leukemic cell in the testis or ovary. This problem seems to be a point of great interest for future study of leukemia.

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EXPLANATION OF FIGURES

Plate 1 Figs. 2–4 show the testis and Figs. 5–7 are the ovary.

Fig. 2. Slight degree of leukemic cell infiltration (AML, 50-year-old male). H.E. ×120.

Fig. 3. Moderate degree of leukemic cell infiltration (AMoL, 30-year-old male). H.E. ×120.

Fig. 4. Marked degree of leukemic cell infiltration (ALL, 17-year-old male). H.E. ×120.

Fig. 5. Slight degree of leukemic cell infiltration (ALL, 9-year-old female). H.E. ×120.

Fig. 6. Moderate degree of leukemic cell infiltration (AML, 45-year-old female). H.E. ×120.

Fig. 7. Marked degree of leukemic cell infiltration (AML, 17-year-old female). H.E. ×120.

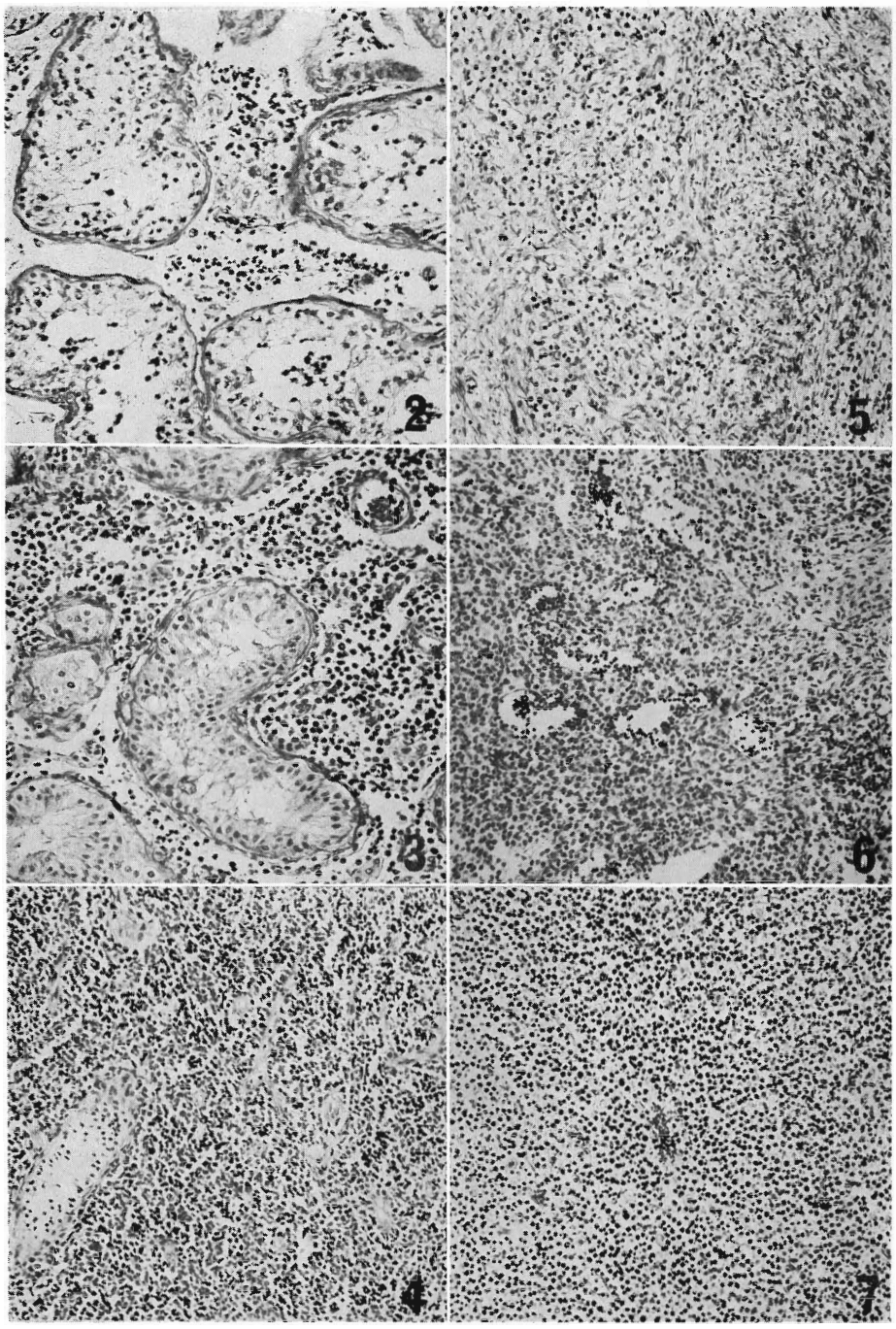
Plate 2 Figs. 8–10: AL, 28-year-old male, Fig. 11: AL, 32-year-old female.

Fig. 8. No leukemic cell infiltration in the bone marrow. H.E. ×300.

Fig. 9. Slight leukemic cell infiltration in the interstital tissue of the testis. H.E. ×120.

Fig. 10. Moderate leukemic cell infiltration in the leptomeninx. H.E. ×120.

Fig. 11. Marked leukemic cell infiltration in the ovary. H.E. ×120.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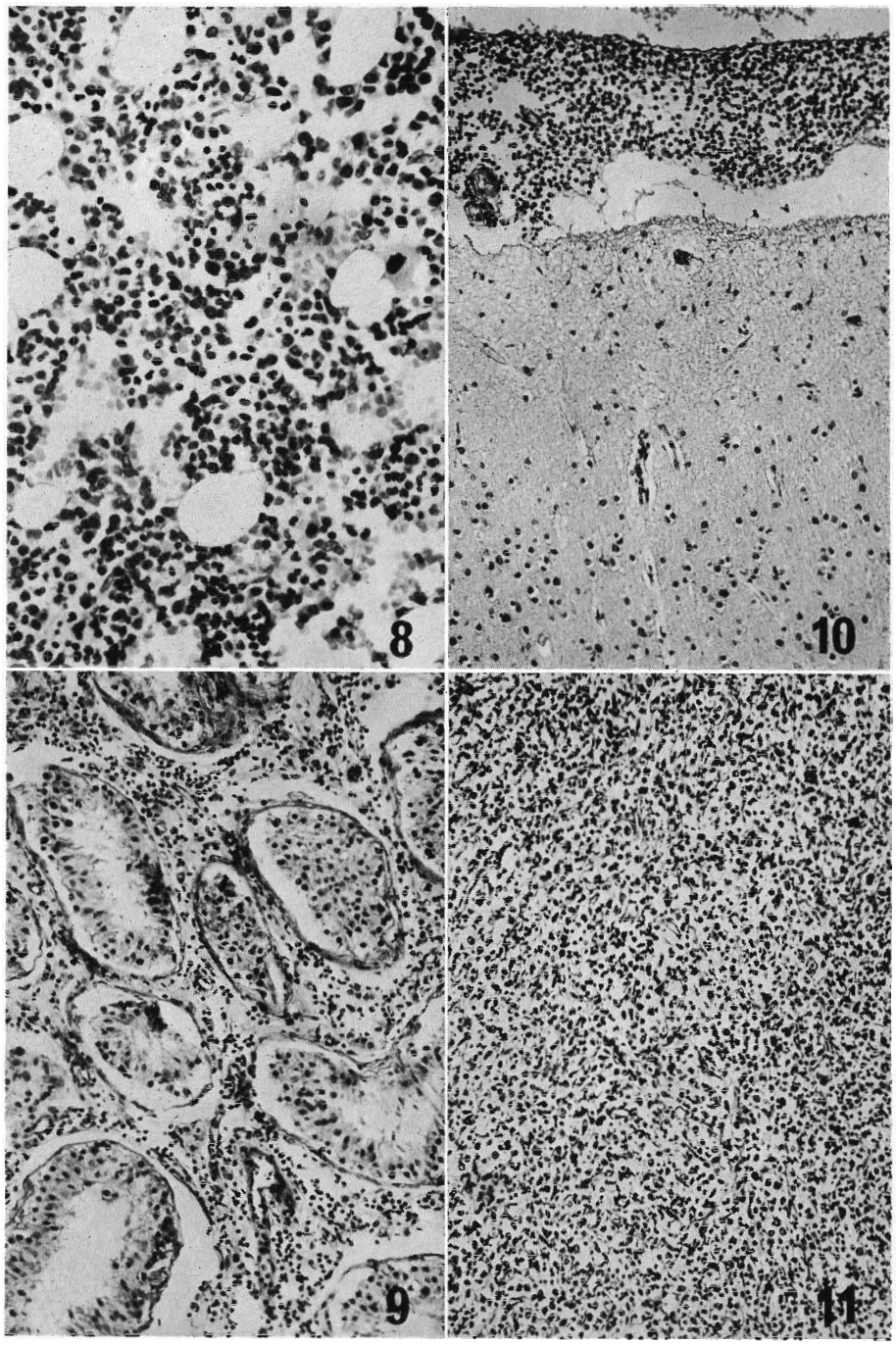
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