Histopathology on Testicular Involvement of Leukemia with an Emphasis on Lymphatics

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WAKASA, H. and AMANO, S. Histopathology on Testicular Involvement of Leukemia with an Emphasis on Lymphatics. Tohoku J. exp. Med., 1977, 123 (2), 147-159 — The human testes in cases of malignant hematopoietic tumors, especially of leukemia, were histologically examined to characterize the mode of leukemic infiltration in comparison with that of malignant lymphoma. Materials were obtained from 56 autopsy cases, composed of 47 of leukemia, 7 of reticulum cell sarcoma and 2 of lymphosarcoma. Leukemic infiltration was confirmed in 43 (19%) of all leukemic cases and the pattern was divided into three types; diffuse, patchy and perivascular. A high grade infiltration was most common in lymphocytic leukemia. The testicular involvement was unexceptionally bilateral with occasional differences in the grade of infiltration, slight to moderate. There was no regional difference in incidence of leukemic infiltration in the testicular interstitium. A thin-walled canal located closely between the proper lamina of seminiferous tubules and the interstitial cell cluster was suggested to be lymphatics, which were extremely irregular in shape and occasionally did not have endothelium. Therefore human testicular lymphatics might not be a constant canal system, but rather akin to narrow tissue space. A network of argyrophilic fibers was pronounced in the lesion of leukemic infiltration. The frequency and grade of an involvement of the testes in malignant lymphoma were lower and lesser than those in leukemia. ——— leukemia; testicular tumor; testicular lymphatics

There have been a small number of reports describing clinical testicular tumor secondary to leukemic infiltration (Gumpesberger and Zimmer 1954; Holzner 1958; Akiyama et al. 1961; Stegagno et al. 1961; Delger and Curueht 1963; Dameshek and Gunz 1964; Matsushita et al. 1966; Sasano and Koizumi 1969). Melicow (1955) reported that there were no cases of testicular tumor due to leukemic infiltration among secondary and/or metastatic tumors of the testicular tissue. In the clinical cases of leukemic infiltration to urogenital organs, Watson and his associates (1949) found one case of limited involvement of the testes.

On the other hand, leukemic infiltration in the testes has been observed not so infrequently in autopsy cases (Hashimoto and Yumoto 1962; Givler 1969). In this paper, it was attempted to elucidate the frequency of testicular involvement, the pattern of leukemic cell infiltration, and the response of testicular interstitial tissue to leukemia. On the basis of an observation on the distribution of leukemic cells in the testes, the pathway of leukemic cells was also examined.

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* Director: Prof. N. Sasano.
Materials and Methods

The materials examined were the bilateral testes obtained from 47 autopsy cases of leukemia in the file of the Department of Pathology, Tohoku University School of Medicine, from 1966 to 1969. These were composed of 33 of myelogenous, 7 of lymphocytic, 6 of monocytic, and 1 of erythremic leukemias.

Among 47 cases, 43 were diagnosed to be acute and 4 were chronic. Age-ranges of the cases were from 6 months to 74 years old. For a comparison, 7 cases of reticulum cell sarcoma and 2 of lymphocytic lymphoma in the above file were also examined.

Bilateral testes fixed in formalin were cut as shown in Fig. 1 and sliced into 4 mm in thickness along the longitudinal axis. According to the usual procedure, paraffin blocks were made and cut 3.5 μm in thickness. The sections were stained with hematoxylin and eosin, Weigert's elastica and Masson's trichrome in every case, and when necessary with Gomori's silver impregnation.

In order to determine the relation of the distribution of leukemic cells to the vascular system in the testicular interstitial tissue, serial sections were made from 2 cases. Leukemic infiltration was identified by the presence of leukemic cells in the interstitial tissue of the testes.

Fig. 1. Sagittal cut of the testis.

Results

Leukemia group

Frequency of leukemic infiltration in the testicular tissue. On gross appearance at autopsy, 5 of 47 cases were diagnosed as having leukemic involvement. In the severely involved cases (Figs. 2, 3), intact tissue was usually not discernible.

Histologic examinations revealed leukemic infiltration in 43 out of 47 cases, or in 91% (Table 1). These 43 cases were composed of 29 myelogenous, 7 lymphocytic, 6 monocytic and 1 erythremic leukemias. Acute leukemia had leukemic infiltration in 39 out of 43 cases and chronic form in all 4 cases. Bilateral testes were involved in 39 cases out of 43 in similar degree. The remaining 4 cases had a difference between bilateral testes in the pattern of involvement; leukemic cells were observed within the vascular lumen on one side, while they were infiltrated into the interstitial tissue through vascular rupture on the other side. A relation of leukemic infiltration to the age of patients was confirmed and leukemic cells were observed predominantly in the age-group from 11 to 40 years old (Table 1).

The degree and mode of leukemic infiltration (Table 2, Figs. 4–9). The pattern
Fig. 2. Gross appearance (severe infiltration). Severe infiltration with replacement of normal architecture.

Fig. 3. Gross appearance (moderate infiltration). Partial leukemic infiltration with hemorrhage.

<table>
<thead>
<tr>
<th>TABLE 1. Frequency of leukemic infiltration and age</th>
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<tbody>
<tr>
<td>Type of leukemia</td>
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<tr>
<td>Myelogenous</td>
</tr>
<tr>
<td>Lymphocytic</td>
</tr>
<tr>
<td>Monocytic</td>
</tr>
<tr>
<td>Erythremic</td>
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<tr>
<td>Total</td>
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* Number of cases of infiltration/number of cases examined

of infiltration was divided into 3 types, diffuse, patchy and perivascular, on the basis of the distribution of leukemic cells. Diffuse and/or severe infiltration was observed in 7 cases out of 43, or in 43% (Table 2). Such a phenomenon was prevalent in lymphocytic leukemia and observed in 3 out of 7. The distribution
Fig. 4. Severe infiltration. Diffuse leukemic cell infiltration in lymphocytic leukemia accompanying compression atrophy of seminiferous tubuli. H.E. × 50.

Table 2. Degree of leukemic infiltration and age

<table>
<thead>
<tr>
<th>Age</th>
<th>Myelogenous</th>
<th>Lymphocytic</th>
<th>Monocytic</th>
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<tr>
<td></td>
<td>Severe</td>
<td>Moderate</td>
<td>Slight</td>
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<tr>
<td>11-20</td>
<td>0</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>21-30</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>31-40</td>
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<td>4</td>
<td>6</td>
</tr>
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<td>41-50</td>
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<td>51-60</td>
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</tr>
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<td>71-80</td>
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<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>3</td>
<td>13</td>
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of leukemic cells in the interstitial space was different from one case to another. In severely infiltrated cases, leukemic cells were diffusely observed in the interstitial tissue with sequent marked widening of the space and remarkable atrophy of the seminiferous tubules (Figs. 4–7).

For the determination of the regional difference in the distribution of leukemic cells, the testes were cut into 3 parts along the longitudinal axis as shown before. The number of infiltrated leukemic cells was counted on each segment in the cases of moderate and slight infiltration. A finding that there was no different distribution in different segments suggested absence of particularly susceptible part for leukemic infiltration. Serial sections made from the case of moderate leukemic infiltration revealed that leukemic cells were present in nodular form in one area, while they were found in perivascular space in another. The finding that the nodular pattern was usually accentuated around the blood vessel suggested a possible rupture of the vascular wall or migration of leukemic cells through it.
The size of such a nodule ranged from 0.5 mm to 1 mm in diameter.

Blood capillaries were always increased in the area of dense infiltration of leukemic cells. Lymphatics, rarely observed in the interstitial tissue of normal testes, were confirmed in the slides revealing leukemic infiltration, closely around the seminiferous tubules (Figs. 10, 11). The lumen of lymphatics was usually surrounded by a thin wall lined with endothelium. There were no red cells in the lumen. The dimension of lymphatics was followed on serial sections by means of projection technique. The lymphatics were confirmed between the proper lamina of seminiferous tubules and interstitial cell cluster. The lumen of the vessel was extremely irregular in shape in individual sections with occasional absence of endothelium. There were occasionally a few number of leukemic cells in
lymphatics.

From the structural characteristics of the vessel, it seems likely that lymphatics might not be consistent channels, but rather akin to narrow tissue spaces.

General aspects. None of the patients had the chief complaint of a testicular tumor due to leukemic infiltration during the course of the disease. In only one case there was pain at the site. Swelling of the testis or an increase in weight was not prominent either. In the cases of moderate involvement of leukemic infiltration, hemorrhage was observed secondary to vascular rupture. In these, the intact tissue was usually preserved partially. The weight and consistency were within the normal range. Frequent mitotic figures in leukemic cells suggested proliferation of infiltrated cells. The tunica albuginea and seminiferous tubules
were beyond the involvement of leukemic infiltration. The formation of argyrophilic fibers was seemingly parallel to the severity of leukemic infiltration in the interstitium (Fig. 12).

In regard to the age relation (Table 2), leukemic infiltration was severe in the group of 16 through 42 years of age compared with those in elder group. The prognosis of the patients was very poor. The clinical courses in the groups with severe and moderate infiltration were 2 to 10 months and 1 to 48 months, respectively.

All of the cases except one had received chemotherapy (Figs. 13, 14), but it was impossible to clarify the influence of the agent on leukemic cells. Possible findings,
related to the influence of the agent were remarkable depletion of spermatogenesis, thickening of the basement membrane of seminiferous tubules, and widespread fibrosis in the interstitial tissue.

A parallel relation between the degree of leukemic infiltration in the testes and peripheral blood seemed to be present in the cases of leukocyte count less than 40,000 at clinical onset. There was no relationship between the degree of leukemic infiltration in the testes and involvement of the liver and spleen (Figs. 15, 16).

**Reticulum cell sarcoma group**

There were no cases having a swelling and pain at the testicular region. Age of the patients ranged from 19 to 65, and 4 were over 50.

Infiltration of sarcoma cells was observed in only one case out of 7. A small number of tumor cells were observed in the interstitium. Argyrophilic fibers were not increased in infiltrated area. Seminiferous tubules were in most cases markedly

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**Fig. 15.** Degree of leukemic infiltration to the liver and testis.

**Fig. 16.** Degree of leukemic infiltration to the spleen and testis.

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Fig. 12. A marked proliferation of argyrophilic fibers forming network frame. Gomori × 200.

Fig. 13. The testis with leukemia, untreated case. Unnoticeable atrophy of seminiferous tubuli and scanty fibrous elements in interstitial tissue. H.E. × 80.

Fig. 14. The testis with leukemia. Treated case. Marked thickening of seminiferous tubuli wall with a decrease of spermatogenesis. H.E. × 80.
atrophic, probably due to administered drug. No relation was observed between tumor cell infiltration of the testes and that of other organs.

*Lymphocytic lymphoma group*

Left testis only was involved in one case of lymphocytic lymphoma, revealing a small nodule. Argyrophilic fibers were increased in number in the involved area.

**DISCUSSION**

Testicular involvement of leukemic infiltration was very frequently observed in autopsy cases, in spite of rare occurrence of leukemic testicular tumor in clinical cases.

Except 4 cases of myelogenous leukemia, all of the cases had leukemic infiltration with or without nodular formation in the testes. There was a tendency that the testes are more reliable to be involved in lymphocytic leukemia than in the other types of leukemia. Such an observation is also supported by the reports of Gumpesberger and Zimmer (1954), Holzner (1958) and Matsushita et al. (1966).

In regard to one of the reasons that the testes were easily involved by leukemic infiltration, Calame (1969) pointed out the presence of extramedullary hematopoiesis during fetal period. He observed extramedullary hematopoiesis in the testes in a frequency as high as 26.5% in 653 cases aged from 0 to 18 years. This occurrence was particularly prominent in infants of first 3 months, but less remarkable after 4 months of age. Several disorders like infection, hypoxemia and blood diseases were considered to stimulate extramedullary hematopoiesis in the testes. The time difference of leukemic infiltration in organs, that is, a later manifestation in the testes than in the liver and spleen, was also suggested by Givler (1969). From these results, the testes seem to be one of the favorite organs for leukemic infiltration like the liver and spleen.

However, against the result of Givler, there was no infiltration in patients younger than 10 years in age in the present study. From our observation that severe leukemic infiltration was observed in the cases from the 2nd to 5th decades suggests a relation of infiltration to the age. As Givler noted, an involvement of the testes by leukemic infiltration was more marked in acute form. He pointed out that an increase in number of the cases of leukemic infiltration in the testes might be associated with the duration of the disease, but his assumption was not supported by the present study.

A consideration that leukemic manifestation in the testes might be induced in the period of remission was advanced by Nies et al. (1965). There was, however, a different report by Mathe et al. (1966) that biopsy of the testes performed in 14 leukemic cases in the period of remission revealed leukemic infiltration in only one case.

The observation of Kostich and Rappaport (1965) that there was no relationship in the degree of leukemic infiltration among the liver, spleen and testes was also confirmed in our series.
Serial sections indicated no significant correlation between leukemic cell group and arterial branches, but a rather continuous extension from this cell aggregation. As capillaries are abundant in these foci, leukemic cells may migrate through capillaries and then infiltrate to the surrounding tissue. The degree of the growth of leukemic nodule seems to have a correlation with a fragility of capillary wall and interstitial fibrosis.

Although abundant lymphatics are easily recognized in submucosal space of tunica albuginea of the testes, the existence of interstitial lymphatics of the testes is highly contradictory. Recently, Fawcett et al. (1969), working with guinea pig and chinchilla testes by the method of perfusion technique of acrolein and glutaraldehyde for the preservation of interstitial contents in situ, demonstrated the lymphatics under electron microscopy. According to his work, interstitial lymphatics are present between tunica propria of seminiferous tubules and Leydig cells or blood capillaries. The lymphatics were hardly visible in usual specimen by light microscopic observation. However, in the present study, thin walled spaces containing leukemic cells selectively were confirmed with light microscopic observation. These spaces are lined with endothelium and present in the above-mentioned area, and they are considered to be lymphatic channels. The shape of lymphatics is variable from one section to another, and it is sometimes impossible to follow them by the continuation of their wall. From these observations, this space may be affected very easily by the condition of surrounding tissue. In our series, leukemic cells have probably been transported via blood stream and then infiltrate to interstitial tissue.

In regard to interstitial response to leukemia cells, Leydig cells were decreased in number in leukemia group (Huseby et al. 1961; Kondo 1962) as compared with those of control group. This is probably due to an occurrence of interstitial fibrosis by leukemic infiltration. Leydig cells containing pigment and vacuoles were increased in number in leukemia group (Tillinger et al. 1957; Ochiai et al. 1958). These features of cells are in accordance with degenerative change of Leydig cells.

It is of interest to notice that tumor cell infiltration in the testes was infrequent in cases of reticulum cell sarcoma and lymphocytic lymphoma. Givler found 5 positive cases in 30, and Cohen et al. (1955) 3 in 47, or in 17% and 6%, respectively. Its frequency in our series was 14%, a value between these two results.

**Conclusion**

A high frequency of leukemic infiltration, encountered in 91%, was confirmed in leukemic cases and the pattern of the infiltration was divided into diffuse, patchy and perivascular. In a group with severe infiltration, there was a marked widening of the interstitial tissue and atrophy of the seminiferous tubules secondary to leukemic infiltration. A high grade of infiltration was observed commonly in lymphocytic leukemia cases. An observation of serial section revealed that there was no particular area suitable for leukemic infiltration in the testes.
A pronounced proliferation of argentophilic fibers was present in accord with the area of leukemic cells.

A distinct tissue space located between tunica propria of seminiferous tubules and interstitial cells was found in leukemia group. This thin-walled canal was suggested to be lymphatics, even though extremely irregular in shape.

The grade and frequency of malignant lymphoma involving testes were strikingly lower than those of leukemia.

References


