CONCISE REPORT

Histopathology of the Thymus of Patients With Acute Lymphoblastic Leukemia and Lymphoblastic Lymphoma in Complete Clinical Remission

By H. Rappaport, D. Machover, R. Bearman, B. Nathwani, M. G. Lemaigre, G. Santelli, J. M. Verley, C. Canon, and G. Mathe

The histologic features of thymuses from three patients who underwent thymectomy for acute lymphoblastic leukemia or lymphoblastic lymphoma in complete clinical remission are described. The thymuses from all three patients were fibrotic with a variability in the appearance of the lobules. Some of the lobules consisted predominantly of epithelial cells with small numbers of mature appearing lymphocytes, while other lobules were expanded and composed predominantly of cells having morphological features of immature lymphoid cells consistent with residual or recurrent disease.

THE HISTOLOGIC FEATURES of the thymus in patients with acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) in complete clinical remission have been unknown. Thymectomy has been done in a small number of patients with T-cell ALL, based on (1) experimental data that have demonstrated that thymectomy done on leukemia-bearing AKR mice during chemotherapy-induced remissions “... appears to significantly prolong remission duration and increase the number of long term survivors” and (2) the hypothesis “that lymphocytes may be continuously transformed in the thymus by hormonal factors secreted by thymic epithelial cells.” We were unable, however, to find any published reports that describe the histopathologic features of thymuses removed from patients with ALL or LBL in complete clinical remission. It is our purpose to present our morphological observations on three such patients.

MATERIALS AND METHODS

Mononuclear cells from peripheral blood and bone marrow were isolated by Ficoll-metrizoate density centrifugation, washed, and resuspended in Hanks balanced salt solution (HBSS). Formation of E-rosettes and staining for surface immunoglobulin (SIg) were done by the method of Jondal et al., for the SIg, fluorescein-conjugated rabbit anti-human IgY, IgA, IgM, IgG were obtained from Behring. Anti-T-cell globulin was prepared from rabbit anti-human thymocyte globulin by extensive absorption with B-cell chronic lymphocytic leukemia cells. Cells to be tested were incubated for 30 min at room temperature, washed 3 times in HBSS, incubated with fluoresceinated goat anti-rabbit IgG (Institut Pasteur) for 30 min, and washed 3 times.

Monoclonal J5 antibody, which detects the common ALL antigen, was kindly provided by J. Ritz and S. Schlossman. Monoclonal anti-Ia was provided by Dr. L. Nadler and Dr. S. Schlossman. Binding of antibody was measured by use of an indirect immunofluorescence assay and analyzed on a fluorescent activated cell sorter II (Becton-Dickinson). One-million cells were incubated with 150 μl of antibody at a dilution of 1:400 for 30 min. The cells were then washed 3 times and incubated with 150 μl of fluoresceinated goat anti-mouse IgG. The pellet was washed 3 times and at least 4 × 106 cells were analyzed.

Acid phosphatase and β-glucuronidase stains were done in one of the three cases.

CASE REPORTS

Case 1

The patient was a 7-yr-old male who had supraclavicular lymph node enlargement, a mediastinal mass with the superior vena cava syndrome, and a right testicular mass. Biopsy of the supraclavicular lymph node led to a diagnosis of LBL. Peripheral blood, bone marrow, and cerebrospinal fluid were normal. No surface marker studies were done. Treatment with adriamycin, asparaginase, prednisone, and vincristine resulted in a complete clinical remission, with disappearance of the medistinal and testicular masses. Subsequent therapy consisted of central nervous system (CNS) and testicular irradiation as well as additional chemotherapy with methotrexate, 6-mercaptopurine, and vindesine. A thymectomy was done 3.5 mo after the onset of the disease when the patient was in complete clinical remission. He is alive with no evidence of disease 16 mo after diagnosis and 12.5 mo after thymectomy.

The thymus weighed 8.5 g (normal for patient's age: 20–30 g) and was fibrotic. Microscopically, a large amount of fibrous tissue surrounded the lobules, which showed a variable cellular composition: (1) some were atrophic and consisted only of epithelial cells with Hassall's corpuscles; (2) some contained epithelial cells and mature-appearing lymphocytes; and (3) in some lobules, the mature-appearing lymphocytes were surrounded by a mixed cellular proliferation composed of both epithelial cells and lymphoid cells having the appearance of blast cells identical to those observed in the lymph node. Some of these cells had convoluted nuclei.
Fig. 1. Portions of two thymic lobules separated by a thin band of fibrous tissue. The lobule on the left is hypocellular and composed predominantly of epithelial cells (see Fig. 2). The lobule on the right is hypercellular and composed predominantly of lymphoid cells (see Fig. 3) (hematoxylin & eosin, x 50).

Fig. 2. High magnification of lobule on the left of Fig. 1 shows the abundance of epithelial cells with a scattering of small, mature-appearing lymphocytes (hematoxylin & eosin, x 730).

Fig. 3. High magnification of thymic lobule on the right of Fig. 1 shows a predominance of lymphoid cells with only few scattered epithelial cells. Mitotic figures are abundant (arrows) and the lymphoid cells are appreciably larger than the small lymphocytes in Fig. 2. The nuclei of the lymphoid cells show appreciable variations in size and shape and bear no resemblance to normal lymphoid cells. They are interpreted as indicative of involvement of this lobule by lymphoblastic lymphoma (hematoxylin & eosin x 730).
Case 2

The patient was a 15-mo-old male who had bilateral cervical lymph node enlargement and no evidence of a mediastinal mass. A lymph node biopsy showed the node to be replaced by lymphoblasts. Further evaluation revealed involvement of the bone marrow. The peripheral blood was normal. The patient was treated with asparaginase, prednisone, and vincristine. In addition, he received irradiation to the CNS and was maintained in complete remission with 6-mercaptopurine and methotrexate and later with immunotherapy. A complete clinical remission lasted 30 mo. At the end of this period, a routine bone marrow aspirate contained 10% lymphoblasts. Therapy with adriamycin, asparaginase, prednisone, and vincristine was instituted and resulted in a complete clinical remission which lasted for 18 mo, when a second hematologic relapse occurred with 20 x 10^9 lymphoblasts/liter in the peripheral blood. An anterior mediastinal mass was also noted at this time. Surface marker studies done on the peripheral blood revealed both spontaneous E-rosette formation and reactivity of the lymphoblasts to antithymocyte serum. The blast cells were La negative and common ALL antigen negative. A third remission was induced with adriamycin, asparaginase, prednisone, and vincristine. During this remission, a thymectomy was done. Two months after thymectomy, the patient suffered a third hematologic relapse and died.

The thymus weighed 9.8 g (normal for patient’s age: 7–30 g) and was grossly fibrotic. Microscopically, the lobules were separated by dense fibrous tissue. Many of the lobules were atrophic and were composed only of epithelial cells or of epithelial cells and small numbers of mature-appearing lymphocytes (Figs. 1 and 2). Other lobules were enlarged and were diffusely infiltrated by lymphoblasts (Figs. 1 and 3) that occasionally showed punctate acid phosphatase and β-glucuronidase activity. A complete clinical remission was induced with adriamycin, asparaginase, prednisone, and vincristine. Subsequently, she received CNS prophylaxis. She relapsed 10 mo after diagnosis despite maintenance therapy and a second remission was induced with the same drugs. A thymectomy was done while the patient was in her second complete clinical remission. She is alive and well in complete remission 23 mo after the first relapse and 20 mo after thymectomy.

At surgery, the thymus was adherent to the innominate vein and the pleura. It weighed 7.2 g (normal for patient’s age: 17–32 g) and was fibrotic. Sections showed dense collagen separating the lobules, some of which consisted of epithelial cells and mature-appearing lymphocytes. The lymphoid population of many of the lobules, however, consisted predominantly of lymphoblasts. Mitoses were evident.

The clinical data and course of these patients are summarized in Table 1.

### Table 1. Summary of Clinical Data

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Diagnosis</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Sites of Disease at Diagnosis</th>
<th>Clinical Course*</th>
<th>Thymectomy (mo from dx)</th>
<th>Status (mo from dx)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LBL</td>
<td>7</td>
<td>M</td>
<td>+ + - - - - +</td>
<td>CR CR CR</td>
<td>3.5</td>
<td>A(16)</td>
</tr>
<tr>
<td>2</td>
<td>ALL</td>
<td>1.25</td>
<td>M</td>
<td>+ - - + - - -</td>
<td>CR CR R1</td>
<td>54</td>
<td>D(56)</td>
</tr>
<tr>
<td>3</td>
<td>ALL</td>
<td>6.5</td>
<td>F</td>
<td>+ + + + - -</td>
<td>CR CR R1</td>
<td>13</td>
<td>A(33)</td>
</tr>
</tbody>
</table>

*Numbers in parentheses are length of CR in months.
†Thymectomy during this remission (see text).

CR, complete remission; A, alive; D, dead; R, relapse.

LN, lymph node; M, mediastinum; PB, peripheral blood; BM, bone marrow; CNS, central nervous system; T, testes; LBL, lymphoblastic lymphoma; ALL, acute lymphoblastic leukemia.

**Case 3**

The patient was a 6.5-yr-old female who had generalized lymph node enlargement, hepatosplenomegaly, a mediastinal mass with the superior vena cava syndrome, and peripheral blood and bone marrow involvement. The CNS was not involved. Surface marker studies done on the peripheral blood and bone marrow revealed spontaneous sheep red blood cell rosette formation by the lymphoblasts. The blast cells also showed punctate acid phosphatase and β-glucuronidase activity. A complete clinical remission was induced with adriamycin, asparaginase, prednisone, and vincristine. Subsequently, she received CNS prophylaxis. She relapsed 10 mo after thymectomy during this remission (see text).

The thymus weighed 7-30 g and was fibrotic. Sections showed the node to be replaced by lymphoblasts. Mitotic figures are evident (Fig. 3).

### DISCUSSION

Both T-cell ALL and T-lymphoblastic lymphoma are presumed to originate from thymus-derived lymphoid cells. This hypothesis is supported by immunologic and clinical observations. In the three patients reported here, thymuses removed during complete clinical remission contained varying proportions of neoplastic-appearing lymphoid cells. In spite of this, two patients (1 and 3) have no relapse at 12.5 and 20 mo after thymectomy. Patient 2 however, relapsed 2 mo after thymectomy and died less than 1 mo later. It is not possible to determine whether the presence of neoplastic-appearing lymphoid cells in the thymectomy specimens represented a new site of relapse or persistence of preexisting thymic involvement in a microenvironment favorable to the proliferation of neoplastic T cells.

Both ultrastructural and combined ultrastructural-functional studies have shown that the cortex of the thymus is anatomically and antigenically isolated. Thus, it is tempting to speculate that the thymus may be a “sanctuary” for neoplastic T cells. However, unlike the testes and the CNS, the thymus may be the site of origin of the neoplastic cells. If this is correct, their presence in the thymus would indicate
LYMPHOBLASTS IN THYMUS DURING REMISSION

The significance of our observation that neoplastic-appearing lymphoid cells are present in the thymus of patients in complete clinical remission is unclear. It is our purpose here not to advocate the use of thymectomy as a means of eradicating residual disease, but merely to record that such residual disease may exist in patients who are in apparently complete clinical and hematologic remission. Although we believe that the focal clusters of lymphoblasts seen in our thymectomy specimens constitute persistent or recurrent disease, this interpretation should be confirmed in a larger series of cases, not only by morphological studies but also by newer methods. These include cytogenetic studies as well as flow microfluorometric analysis of DNA content.

REFERENCES


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