Failure of Thymectomy to Alter the Subsequent Course of Human Acute Leukemia in Drug-Induced Remission

By Rouben M. Jiji, Milton S. Sacks, Eugene J. Linberg and Carroll L. Spurling

In recent years there has been increasing evidence that the thymus may be the "master gland" concerned with lymphopoiesis and immunity. In the mouse the thymus has been demonstrated to have a significant role in the pathogenesis of leukemia. Several different approaches have emphasized its importance. Thymectomy, in high leukemic strain mice, considerably reduces the incidence of spontaneous leukemia. The incidence of leukemia in hybrid mice bearing a thymic transplant from a high leukemic strain is considerably increased. Radiation-induced lymphoid tumors in low leukemia strain C57 mice are significantly reduced if the mice are thymectomized before irradiation or as late as 12 weeks after irradiation. Lymphomas develop with moderate and reproducible frequency in thymectomized irradiated mice bearing grafts of normal isologous thymus. The incidence of carcinogen-induced leukemia in strain DBA mice is reduced by thymectomy while autologous grafting of the thymus to thymectomized mice raises the incidence to prethymectomy level. Inoculation of passage virus "Gross" agent A induces leukemia in the low leukemia strain C3H mice; however, the incidence of leukemia is remarkably reduced when the mice are thymectomized. Similarly, thymectomy in the high leukemic AKR strain, performed at the age of 3 to 4 weeks of life, prevents the induction of premature leukemia by Gross agent A inoculation.

Very little information is available as to whether the thymus has a comparable role in human leukemogenesis. Dean et al., in 1951, reported that thymectomy in previously untreated children with acute and subacute lymphocytic leukemia failed to induce remission. Soutter and Emerson performed elective thymectomy in a 57-year-old man with regenerative anemia associated with monocytic leukemia. The patient died 8 months postthymectomy, and the postmortem bone marrow findings were said to be typical of monocytic leukemia.

With these observations in mind, we decided to conduct a limited pilot study on the effect of thymectomy on the course of human leukemia. It is obvious that one must be cautious in applying the results of animal studies directly to human disease. However, it appeared that extirpation of the thymus during the period of drug-induced remission might simulate to some degree the experimental model in mice. To the best of our knowledge, no similar attempt under these conditions has been made previously.

After the induction of complete clinical and hematologic remission by accepted chemotherapeutic means, thymectomy was performed in 3 patients...
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with acute leukemia—two lymphocytic and one, erythromyeloid. Peripheral blood and bone marrow aspirates revealed no apparent stigmata of leukemia prior to thymectomy. There was no apparent beneficial effect of thymectomy under these conditions and the study was not continued. It is the purpose of this communication to report the negative results obtained.

CASE REPORTS

Case I (S. J., University Hospital #17-18-80). A 16-year-old white boy was admitted to the University Hospital on January 23, 1959 complaining of headache, progressive weakness, and low grade fever of 2-weeks duration. The past history was not remarkable. Pertinent physical findings consisted of marked pallor and a palpable spleen which extended four finger-breadths below the left costal margin. There was no hepatomegaly and no lymphadenopathy. No hemorrhagic manifestations were present. The hemoglobin was 6.4 Gm. per cent, the platelet count 18,000 per cu. mm., and the white blood cell count 12,300 per cu. mm. There were 30 nucleated red blood cells per 100 white blood cells. In the differential count there were 20 filamented neutrophils, 1 nonfilamented neutrophil, 48 lymphocytes, 4 monocytes, 16 metamyelocytes, 6 promyelocytes and myelocytes, and 5 myeloblasts. Uric acid was 10.2 Gm. per cent. Bone marrow examination revealed a hypercellular smear with marked reduction in the megakaryocytes; there was 50 per cent megaloblastoid erythroblasts, 15 per cent myeloblasts, and 15 per cent promyelocytes. The hematologic picture was considered to be characteristic of acute erythromyeloid leukemia.

Complete remission, both clinical and hematologic, was achieved after 6 weeks of therapy with 6-mercaptopurine, 150–200 mg. daily. On discharge the spleen could not be felt. The hemoglobin was 16.0 Gm. per cent and the white blood cell count was 6500 with a normal differential cell count. The remission persisted for the next 10 months. During remission he was maintained on 6-mercaptopurine, 850 mg. weekly.

Thymectomy was performed uneventfully on June 11, 1959 when he was in complete remission. The surgical specimen consisted of 2 pieces of lobulated thymic tissue, one measuring 10 X 6 X 1 cm. and the other 3 X 2 X 1 cm. Microscopic examination revealed thymic tissue which was moderately atrophic.

The patient continued to do well both clinically and hematologically until January 1960. Subsequently he became anemic and serial peripheral blood smears revealed the reappearance of nucleated red blood cells and a progressive increase of myeloblasts. Serial bone marrow examinations demonstrated progressive increase in the proportion of myeloblasts. A short course of Aminopterin and a longer trial of Vincaleucoblastine were tried without success. The patient died on January 31, 1961, 18 months post-thymectomy and 24 months after the diagnosis of leukemia had been made.

Case II (J. A., University Hospital #19-54-94). This 4-year-old white girl was hospitalized in September 1959 because of recurrent pain in the joints and fever. The only pertinent physical finding was moderate pallor. There was no lymphadenopathy, hepatosplenomegaly, or hemorrhagic manifestations. The patient’s sister had died in 1956 of acute lymphocytic leukemia. The mother had x-ray pelvimetry during the eighth month of pregnancy with this child. The hemoglobin on admission was 8.7 Gm. per cent, the white cell count 8200 per cu. mm., and the platelet count 660,000 per cu. mm. The differential count revealed 80 per cent lymphocytes. Bone marrow examination showed a predominance of lymphoblasts and a marked reduction of megakaryocytes.

Complete remission was achieved with Prednisone 60 mg. daily. She was subsequently maintained on prednisone 10 mg. and 6-mercaptopurine 50 mg. daily. Prior to thymectomy the hemoglobin was 14.5 Gm. per cent, the platelet count 1,500,000 per cu. mm. and the white blood count 9750 per cu. mm. with a normal differential count. The bone marrow examination was normal.

Thymectomy was performed on January 21, 1960 after 1 month of complete remission.
The surgical specimen measured 7 × 3 × 0.7 cm. Microscopic examination revealed a markedly atrophic thymus.

The child did well for 6 months after the operation. However, in June, 1960 she started complaining of severe back pain. Lymphoblasts and young lymphocytes were again noted in the peripheral blood. Repeat bone marrow examination showed a predominance of lymphoblasts. A trial of Vincaleucoblastine failed to induce remission. Partial remission was subsequently achieved with Aminopterin, 0.25 mg. daily. The back pain decreased in intensity, and peripheral blood and bone marrow pictures showed a decrease in lymphocytic elements. She ultimately expired with clinical and hematologic signs of acute lymphocytic leukemia on February 27, 1961, 18 months after the diagnosis of leukemia had been made and 14 months after thymectomy.

**Case III** (M. C. J., University Hospital #18-41-28). A 3-year-old white girl was admitted to Mercy Hospital, Baltimore, on January 27, 1959 because of joint pains and fever of 5 days duration. The pertinent clinical findings consisted of pallor, moderate cervical lymphadenopathy, and slight hepatosplenomegaly. The hemoglobin was 10.2 Gm. per cent, the white blood count 31,900 per cu. mm., and the platelet count 14,000 per cu. mm. In the differential count there were 5 filamented neutrophils, 4 nonfilamented neutrophils, 1 myelocyte, 5 monocytes, 2 eosinophils, 2 metamyelocytes, 20 lymphocytes, 13 prolymphocytes, and 48 lymphoblasts. Bone marrow examination revealed a predominance of lymphoblasts and virtual absence of megakaryocytes.

Complete remission was achieved with prednisone 60 mg. daily. She was subsequently maintained on prednisone 5 mg. and Aminopterin 0.125 mg. daily. However, 2 months later she again started to complain of joint pains and became febrile. The white blood count rose to 20,000 per cu. mm. and lymphoblasts again appeared in the peripheral blood. Prednisone was increased to 40 mg. daily and 6-mercaptopurine, 50 mg. daily was started. Aminopterin was discontinued. A second complete remission occurred. Examination of the bone marrow at this time was normal.

Thymectomy was performed on July 21, 1959. Microscopically the thymus was markedly atrophic.

Following thymectomy the patient was maintained on prednisone 15 mg. and 6-mercaptopurine 25 mg. daily. She continued to do well until 4 months post-thymectomy. At this time the white blood count rose to 84,000 per cu. mm. and lymphoblasts were prominent in the differential count. Shortly thereafter she died at home with a generalized bleeding tendency. The total course of the disease was 8 months.

**DISCUSSION**

Thymectomy apparently failed to alter the course of the disease in these 3 patients. The patient with acute erythromyeloid leukemia died 18 months after thymectomy and 24 months from the time of diagnosis. The 2 patients with acute lymphocytic leukemia died 4 and 14 months post-thymectomy and 8 and 16 months from the time of diagnosis. The survival in these 3 cases falls within the range reported in the literature. The short remission and survival in Case III conforms to the known poor prognosis of patients with an initially high white cell count. Because the procedure produced no striking benefit, we did not feel justified in pursuing it further. The small series, of course, makes comparison with controls impossible.

The negative results reported here do not necessarily exclude the possibility of a thymic role in human leukemogenesis. It can be postulated that the cellular elements of the hematopoietic system, even though morphologically normal as a result of drug-induced remission, are still potentially leukemic and therefore retain their autonomy from thymic influence. Further, the thymus may influence only certain types of leukemias and not others. Some
mice inoculated with the leukemia virus and thymectomized develop late in life an atypical leukemia of myeloid origin. In this connection, Metcalf\textsuperscript{22-25} reported that overactivity of thymus lymphocytosis stimulating factor is present in high leukemia and postirradiated low leukemia strains of mice, and in patients with chronic lymphocytic leukemia. The role of the thymus in leukemogenesis may be confined to neonatal and early postnatal life. Thymic extirpation experiments performed on animals (mice, rabbits, rats, and golden hamsters) demonstrate that thymic dependency of lymphopoiesis and immunity does not persist beyond early postnatal life.\textsuperscript{26-34}

**Summary**

Thymectomy was performed during the period of drug-induced remission of acute leukemia in 3 patients aged 16, 4, and 3 years. One case was characterized as acute erythromyeloid and 2 as acute lymphocytic leukemia. In each instance thymectomy apparently failed to influence the subsequent course of the disease. From these limited data, it does not appear that further experience with this procedure is warranted at the present time.

**Summario in Interlingua**

Thymectomia esseva effectuate durante un periodo de remission pharmaco-\-gene in 3 patientes con leucemia acute de 16, 4, e 3 annos de etate. In 1 del casos il se tractava de acute leucemia erythromyeloide, in le altere 2 de acute leucemia lymphocytic. Il pareva que le thymectomia non influentiava le curso subsequente del morbo in ulle del 3 casos. A base de iste restrigite datos, il non pare justificate cercar experientias additional in le uso del procedimento mentionate.

**ADDENDUM**

After completion of this report our attention was called to an abstract of a paper in the Russian literature\textsuperscript{35} dealing with thymectomy in a child with acute leukemia in remission. The effect of thymectomy was not noted.

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