LYMPHATIC LEUKEMIA WITH THYMIC ENLARGEMENT: A BRIEF REVIEW OF THE LITERATURE WITH CASE REPORTS

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Slight enlargement of the thymus may perhaps be present in lymphatic leukemia more frequently than is recorded in the literature. This enlargement may be a true lymphosarcoma or thymoma, or only a hyperplasia of lymphoid tissue.

In a considerable series of cases a large sarcomatous tumor of the thymus with a leukemic blood picture has been the chief feature, so that leukemia with involvement of the thymus came to be recognized as an atypical and malignant variety (1). These growths have been designated by Orth as malignant leukemic lymphoma (2).

As noted by Kaufmann (3), "in leukemia, marked enlargement of the thymus gland is occasionally seen, especially in acute lymphatic leukemia."

The rapid growth of the thymus may be out of all proportion to the hyperplasia of other lymphatic structures and to the blood picture, thus giving rise to a mistaken diagnosis of thymoma as an entity. As stated by Heubner (4), "with thymic tumors the other lesions of leukemia have not always been fully developed."

Milne (5) in 1913 reported an unusual case of lymphatic leukemia which at autopsy revealed a mass of hyperplastic lymphoid tissue in the upper mediastinum, attached to the pericardium. This mass was ascribed to a hyperplasia of the anterior mediastinal lymph nodes and most probably the thymus, though no Hassall’s corpuscles could be demonstrated.

In 1925 Friedlander and Foote (6) reported a case of "malignant small-celled thymoma with acute lymphoid leukemia." Here the unripe lymphoblasts of the blood stream so closely resembled the cells of the thymic tumor found at autopsy that the question arose—was the source of the abnormal cells of the blood an outbreak of the tumor through the wall of some vein, or was the whole
process true lymphoid leukemia? This question was not definitely decided.

de Lavergne, Abel and Debenedetti (7) have recently reported a case which presented a tumor of the anterior mediastinum with clinical symptoms of acute leukemia. Radiography demonstrated a non-pulsating mass which extended beyond the sternum on either side to enclose the cardiac shadow. At autopsy a large gray mass adherent to the posterior surface of the sternum occupied the whole anterior mediastinum and was attached to and displaced the adjacent structures. Microscopic examination of this tumor revealed homogeneous sheets of small lymphocytes and a few macrolymphocytes. No Hassall's corpuscles were found, but these are not essential diagnostic features of thymic tumor (8). The distribution of the lesions did not support the idea of a primary neoplastic process in the thymus. There was no actual invasion or destruction of the pericardium, great vessels, or sternum, and there was a generalized lymphadenopathy. The final diagnosis, therefore, was subleukemic lymphomatosis, possibly an acute terminal exacerbation. The authors note that with the low percentage of neutrophilic polymorphonuclear leukocytes (3 per cent), there was an actual as well as a relative agranulocytosis. Aubertin and Levy have shown that there is a whole sequence of processes between "pure" agranulocytosis and the lymphomas (9).

Recently, Emile-Weil, Isch-Wall and Bertrand (10) have reported a case of leukemia with a mediastinal tumor. The presence of a large anterior mediastinal mass, indicated clinically, was confirmed by a roentgenogram. The presumptive clinical diagnosis was pericardial effusion, possibly tuberculous, but the results of pericardicentesis were negative. The blood count showed leukemia with the differential count almost entirely *cellules souches indifférenciés* (primitive undifferentiated cells, which are regarded by the French as pathognomonic of acute leukemia). Autopsy revealed an enormous white mass enveloping the heart and lungs, which were pushed upward into the superior portion of the thorax. Histologically the tumor was composed of cells resembling lymphocytes, but with larger, clearer nuclei. The lymph nodes, spleen, liver, and kidneys were infiltrated by the same type of cell. The bone marrow was completely transformed by infiltration with the same type of cell.

In 1912 von Müllern and Grossmann (11) reported a case of an
acute leukemic myelosis in a child five years of age, with a rapidly fatal termination. The lymph node enlargement, though limited in degree, was generalized. At autopsy an enlarged thymus was found with a marked development of the whole lymphatic system. Histologically, the myeloid tissue was found to be greatly developed in the liver and spleen, but there were no myeloid elements in the lymph follicles. There were atypical forms of myelocytes and myeloblasts, such as are rarely seen in typical myeloid leukemia, yet nowhere was there any atypical, aggressive growth.

Haenisch and Querner (12) in 1916 reported a case of enlarged thymus in lymphatic leukemia. The adenopathy was generalized but not excessive except in the tonsils. The white blood count was high, the differential count showing a preponderance of medium-sized lymphocytes. Autopsy revealed a huge tumor in the upper mediastinum, flat and lobulated, resembling the thymus in shape. The tumor consisted of soft, elastic, light gray masses, of rather homogeneous appearance on section. Microscopically the lymph nodes and the thymus consisted of small lymphocytes with either no visible cytoplasm or a very narrow rim of cytoplasm and a delicate stroma between the cells.

Between the years 1910 and 1920, 32 cases of acute and chronic lymphatic leukemia were seen at the Mayo Clinic, in which complete post-mortem examinations were made (Margolis, 13). These were divided into two groups, those with and those without thymic enlargement. The second group, with enlargement of the thymus, was composed of four cases (12 per cent), three of which were in children and the fourth in a man twenty-three years of age. Three of these subjects presented the picture of rapidly progressive acute lymphatic leukemia. In addition to generalized lymphocytic accumulation within various tissues, there was a tendency to maximal infiltration in only one or two sites, such as the mediastinal structures and the kidneys. Section of these mediastinal masses failed to show any reticulum or Hassall's corpuscles. Margolis' conclusions were that "the thymus gland is rarely enlarged in lymphatic leukemia, the predominant tendency in this disease being in the direction of involution of the organ. Enlargement of the thymus gland is not due to hyperplasia of the small thymic cells but to infiltration by lymphocytes, the process being identical with that leading to infiltration of other non-lymphoid organs."

There have recently occurred on the medical service of the Memorial Hospital, four cases of lymphatic leukemia accompanied
by thymic enlargement, the diagnoses of which were established by x-rays. In one case the diagnosis was confirmed by autopsy.

CASE REPORTS

CASE I. H. L., a male child aged six years was admitted to the clinic on March 10, 1928. About six months before, the mother had noticed that the child seemed to tire easily and that he often complained of pain in his legs. Two and a half months before coming to the clinic he developed a severe bronchitis which lasted seven to ten days and recurred one week later with symptoms of "croup." This, however, cleared up, and the child was apparently well until two weeks before coming to the hospital. At that time nausea with occasional vomiting, loss of appetite, and constipation appeared. At the same time the mother noticed nodules in the neck and in both groins. Nose-bleed became frequent, and black and blue spots without previous injury developed on the legs. The child lost three pounds in weight in the two weeks preceding admission to the clinic.

The family history was negative. At seven months of age the child had had bronchitis, which had recurred at infrequent intervals. At the age of one year he had had an otitis media which required a myringotomy. A tonsillectomy had been performed at fifteen months.

Examination showed a pale and undernourished child. The eyelids, both upper and lower, showed some puffiness. Several petechial hemorrhages were present on each cheek. The tonsils had redeveloped with an appearance of infiltration upward involving the anterior tonsillar pillars. The heart rate was 118; a soft systolic murmur was audible at the apex. By percussion it was found that the mediastinum was considerably broadened, particularly to the right, the dullness extending to the mid-clavicular line. D'Espinels's sign was well marked. The spleen extended two finger breadths below the costal margin, and the liver nearly to the iliac crest. The lower extremities showed several old ecchymotic areas. The lymph nodes of the neck, axillae, and groins showed generalized enlargement. The occipital and epitrochlear nodes were also involved.

An x-ray film of the chest (Fig. I) showed a clean cut dense mass in the mediastinum, presenting the features of a thymoma.

On the same day a low-voltage x-ray treatment—a very small fractional dose—was given to the thymic region. The blood count when first taken showed hemoglobin 50 per cent; red blood cells 2,800,000; white blood cells 58,000. The differential count showed small lymphocytes 98 per cent; polynuclear cells 1 per cent; transitional cells 1 per cent.

The patient returned to the clinic four days later, his general condition greatly improved. However, the blood count then showed a hemoglobin of 35 per cent; red blood cells 1,760,000; white blood cells 1,800. The differential count showed small lymphocytes 87 per cent; large lymphocytes 5 per cent; polynuclear cells 8 per cent. This very sudden and marked drop in the white and red cell counts contraindicated further irradiation, and the patient was admitted to the hospital on the following day for observation.
Ten days after x-ray therapy, a film of the chest showed marked diminution in the size of the mediastinal mass (Fig. 2). Subsequent films showed no appreciable change.

Blood counts at three- to four-day intervals showed a gradual rise in the white cell count, and on March 30, three weeks after the x-ray therapy, the red cell count was 1,720,000; the white cell count was 128,000, with 99 per cent small lymphocytes and 1 per cent polynuclear cells.

At this time the first of six blood transfusions was given. During the months of April and May, three x-ray treatments were given, one to the nodes of the right neck, one to the nodes of the left neck, and one to the splenic area.

The general condition of the patient gradually became worse and he died on June 9, three months after admittance to the hospital.

Autopsy revealed a diffuse lymphoma of the thymus, with a diffuse lymphocytic hyperplasia of the tonsils and lymph nodes and lymphocytic infiltration of the kidneys, spleen, lungs, heart muscle, liver, and pancreas.

Microscopically the liver showed a rich infiltration in the portal canals and capillaries, with large mononuclear cells resembling leukocytes. Section of the lung revealed a beginning pneumonia. The lymph nodes and tonsils showed a diffuse hyperplasia. The heart muscle showed a lymphosarcomatous deposit in the pericardium and muscle. The intestine was negative. The kidney revealed diffuse lymphosarcomatous infiltration.

There were no specific features of thymoma.

**CASE II.** F. S., a newsboy aged fourteen years, was admitted to the Memorial Hospital on Jan. 26, 1931, with the complaint of difficulty in breathing and in swallowing, swelling of the face, neck, and chest, cough and headache, and a mass over the upper portion of the sternum. This mass was first noticed three months before and had increased in size rapidly. For the two weeks preceding his admission to the hospital, the
The patient had been unable to sleep because of difficulty in breathing and an almost constant cough. Cyanosis became very pronounced on the slightest exertion. The swelling of the face and neck had not been observed until nine days before he came to the hospital.

The family history was entirely negative. Three brothers and two sisters were well.

The patient's past history showed whooping cough and measles in infancy. During the past three or four years he had suffered from headaches, at times severe, lasting two to three hours. However, no treatment had been instituted, nor had a complete physical examination been made.

Physical examination showed a well developed and fairly well nourished boy, fourteen years of age, weighing 125 pounds. The skin showed a petechial rash over the trunk anteriorly and posteriorly, particularly marked over the flexor surface of the forearms. Grossly this rash resembled measles. It could not be determined how long it had been present. The eyes were normal. There was some tenderness over the frontal sinuses, and an acute serous nasal discharge. The teeth were in fair condition, the tonsils normal. The heart rate was 132, with no irregularities or murmurs. Breath sounds over the left apex were bronchial. The abdominal findings were negative. Examination of the extremities showed nothing unusual. Knee jerks could be elicited only by reinforcement.

There was a large, mound-like protuberance over the upper portion of the sternum (Fig. 3). It was firm and non-compressible, and had an irregular surface. The mass extended two-thirds of the distance down the
sternum. On percussion the mediastinum was definitely widened, extending on the right to the costochondral junction above and to a less extent below. On the left it extended slightly beyond the mid-clavicular line above, and merged with the heart dullness below. D'Espine's sign was marked. There was a dilatation of veins of the anterior chest wall, extending down to the upper abdomen. There was a marked fullness at the base of the neck anteriorly and in the left supraclavicular space. A few small nodes were palpable in the left lower neck anteriorly, and several larger nodes in each axilla.

Blood count on admission showed hemoglobin 80 per cent; red blood cells 4,140,000; white blood cells 16,400; with a differential of 8 per cent polymuclear cells; 67 per cent large lymphocytes; 42 per cent small lymphocytes; 2 per cent transitional cells.

Urinalysis was negative.

X-ray of chest showed a mass in the upper part of the mediastinum projecting into the right chest for a distance of 3 cm. (Fig. 4).

An aspiration biopsy of the tumor mass failed to show any tumor cells.
Two days after his admission to the hospital the patient received a high-voltage x-ray treatment to the tumor, over an area 10 x 10 cm. On the same day he suffered a severe bilateral nasal hemorrhage which necessitated post-nasal packing. A hypodermoclysis of 1500 c.c. was given. On the following day the packing was removed, after which a thin serosanguineous discharge flowed from the nostrils. Calcium chloride was given intravenously and thromboplastin intramuscularly. On Jan. 29 the blood count showed hemoglobin 50 per cent; red blood cells 2,800,000; white blood cells 14,800; with a differential count of 6 per cent polynuclear cells, 54 per cent large lymphocytes, and 40 per cent small lymphocytes.

Nasal bleeding recurred, and a transfusion of 600 c.c. of whole blood was given, following which the hemorrhage decreased.

Following the x-ray therapy the regression of the tumor was marked, but because of the decrease in red blood cells, further radiation was delayed.

On Feb. 3 the nasal hemorrhage recurred but was controlled by packing. A second transfusion was given and a high-voltage x-ray treatment was given the nose and cheek area in an effort to prevent further hemorrhages. Calcium chloride and thromboplastin were again administered, and these measures appeared to control the bleeding. On the two succeeding days slight nasal hemorrhages occurred, requiring packing, but on the morning of the 7th, bleeding became more profuse, and could not be controlled. The weakness and dyspnea became more marked, and the patient expired. An autopsy could not be obtained.

**CASE III.** H. B., an insurance clerk, aged thirty-five years, applied for treatment Oct. 31, 1930. His main symptoms were loss of weight and a troublesome cough. At times he had some pain in the right lower chest. Some little time before coming to the hospital he had noticed enlargement of the nodes of the left neck. Later, nodes in the right neck and in both groins were observed. At the time of an appendectomy, eighteen months before, a node had been observed above the left clavicle but was regarded at that time as insignificant. The patient had lost 23 pounds during the previous six months.

The patient's mother had died at the age of forty-two years, of cancer of the breast. His father had died at sixty-six, cause unknown.

Physical examination showed a young adult male, rather pale and somewhat undernourished. On x-ray examination the two lower left bicuspids had shown focal infection. Extraction of these teeth had been advised. The tonsils were moderately enlarged. The heart was slightly enlarged on percussion. There was some decrease of breath sounds, with a few crackling râles at the base of the right lung posteriorly.

Abdominal examination showed a general resistance and fullness throughout the central portion. The spleen was enlarged to four finger breadths below the costal margin. In the right upper abdominal quadrant a mass was palpable which suggested a mass of lymph nodes rather than an enlarged liver.

There was generalized lymph node enlargement in both sides of the
neck, both axillae, and both groins. In places these nodes appeared to be matted together. The occipital nodes were also involved. Definite sternal tenderness was present.

An x-ray film of the chest (Fig. 5) revealed evidence of a clean-cut mass of homogeneous density in the right chest, bulging from the lower mediastinum downward into the right thorax, which it almost completely filled, without displacing the heart to the left. The right border of the heart could not be distinguished. Stereoscopic films showed the mass to bulge more posteriorly than anteriorly.

The blood count on admission to the clinic was: hemoglobin 90 per cent; red blood cells 4,560,000; white blood cells 16,400, with a differential count of 35 per cent polynuclear cells; 10 per cent large lymphocytes; 51 per cent small lymphocytes; 3 per cent eosinophile cells, and one per cent basophile cells.

The mediastinal mass was treated with x-rays, the doses being fractionated in order to avoid a severe reaction. Following this course of therapy an x-ray film of the chest (Fig. 6) revealed a marked diminution in the size of the mediastinal mass. The white blood count at that time was 8,500, with a differential count of 44 per cent polynuclear cells; 17 per cent large lymphocytes; 37 per cent small lymphocytes, and 2 per cent transitional cells.

The patient's general condition improved. X-ray therapy, which had been directed entirely toward the chest area, was continued over the nodes of the groins, axillae, and neck. Thesesoon decreased in size, some disappearing entirely.

Subsequent chest films showed only diminution in the size of the mediastinal mass until Dec. 11, 1930, when a film showed a slight increase
in size. X-ray therapy over the chest anteriorly and posteriorly was then repeated.

The last blood count, taken on May 1, 1931, showed: hemoglobin 80 per cent; red blood cells 4,190,000; white blood cells 5,600 with a differential count of 68 per cent polynuclear cells; 15 per cent large lymphocytes;

5 per cent small lymphocytes, 10 per cent transitional cells, and 2 per cent eosinophile cells.

At the present time the patient is in good health and has gained 40 pounds in weight. There is only slight superficial adenopathy. The mass in the right upper quadrant of the abdomen has disappeared.
CASE IV. R. M., a male infant aged thirteen months, was brought to the clinic on June 10, 1931. Seven weeks before, the child had fallen and bruised its forehead. The swelling had receded, then returned again in the next few weeks. The affected area had not been tender until about two weeks before. The child had been fretful at night.

Examination showed a normal child with a tumor of the left frontal and temporal area, hard, non-pulsating, extending posteriorly to the ear and downward over the temple. There was also a tumor over the left mandible. Further examination was entirely negative. No adenopathy was found.

Blood examination showed: hemoglobin 80 per cent; red blood cells 4,450,000; white blood cells 16,200 with 41 per cent polynuclear cells, 11 per cent large lymphocytes, 29 per cent small lymphocytes, 17 per cent transitional cells, and 2 per cent eosinophile cells.

Radiographic examination showed an enlarged thymus (Fig. 7). There was no evidence of any definite bony destruction in the skull, but cortical thickening and periosteal changes in the femora and the tibiae were found.

A diagnosis of lymphatic leukemia with bone involvement and an enlarged thymus was made.

X-ray treatments were given to the cranium and skeleton. The white blood count on June 15, 1931, three days after x-radiation was: white blood count 10,400 with 20 per cent polynuclear cells, 10 per cent large lymphocytes, 50 per cent small lymphocytes, 2 per cent transitional cells, and 18 per cent fragile undifferentiated cells. The swelling of the forehead shrank appreciably in three days. The left eyelid which had been closed was then partly open. Later the child was taken to another hospital, where he died five months after the onset of symptoms. An autopsy was not obtained.

DISCUSSION

In Cases I and II, occurring in young individuals, the leukemic process was evidently of a more acute type, as manifested by the short previous duration, the hemorrhages, the effect of irradiation in producing a startling drop in the leukocyte count as in Case I, or uncontrollable hemorrhage as in Case II, and finally the rapid course subsequent to irradiation. It was startling to see in Case I a drop in the white cell count in four days from 58,000 to 1,800 following an x-ray dose which ordinarily would be considered very small. In each of the reported cases, except the last, a broadening of the anterior mediastinum was demonstrated by percussion, and in Case II a mass over the sternum indicated penetration of the chest wall by the tumor.

In each case roentgenography showed the presence of a mediastinal mass, probably of thymic origin. Unfortunately Case II
reached a fatal termination before the effects of radiation upon the thymic tumor could be noted. Cases I and III showed a decrease in the size of the tumor mass following this therapy. In Case IV it is impossible to draw conclusions as to the result of therapy, since the patient failed to return for observation and died later in another hospital.

**Conclusions**

1. Tumefaction of the thymus in association with lymphatic leukemia, while rare, is a definitely recognized variant of that disease and is probably the result of leukemic infiltration of the organ.

2. In cases of thymic tumor the blood and lymph node system should be carefully observed for evidence of leukemia.

3. The thymic tumors associated with lymphatic leukemia are radiosensitive.

4. In younger individuals the leukemic process is likely to be of a more acute type. Therefore, while the disease is responsive in some measure to irradiation, great caution in selection of dosage is needed to avoid precipitating such exacerbations as an increase of a hemorrhagic tendency or an acute leukopenia. When a hemorrhagic tendency or a leukopenia is already established it would seem best to withhold treatment until one can judge the gravity and acuteness of the disease.

**References**

2. Orth. Quoted by Ewing.