LYMPOCYTIC LEUKEMOID REACTION OF THE BLOOD ASSOCIATED WITH MILIARY TUBERCULOSIS

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Blood pictures similar to those of myelocytic and lymphocytic leukemia have been reported to occur not infrequently in patients with miliary tuberculosis. These reports indicate that there is a marked "shift to the left" of the leukocytes in the peripheral blood to include varying percentages of myelocytes and myeloblasts. This hemogram is associated with an absence of the characteristic leukemic infiltration of the tissues on postmortem examination.

Landon has reported a case of tuberculous bronchopneumonia in a 16 year old girl in whom the white blood cell count rose to 36,800 per cubic millimeter of blood; 95 per cent of the cells were considered to be immature lymphocytes. Coley and Ewing has reported the case history of a 42 year old woman with diffuse tuberculosis of the lymph nodes. The white blood cell count was 8,000 cells per cubic millimeter of blood, of which 84 per cent were reported as of the "mononuclear" type. The mononuclear cells were considered to be lymphocytes. The structural changes in the lymph nodes showed acute necrosis without caseation and without tubercle formation.

Leibowitz has reported the occurrence of a predominantly myeloblastic blood picture in a patient with symptoms of sepsis associated with miliary tuberculosis. Examination of tissues removed from various organs showed necrotic lesions containing myriads of tubercle bacilli but without tubercle formation.

One case with a monocytic leukemoid reaction has been studied. The patient showed a white blood count of 82,000 cells per cubic millimeter of which 42 per cent were monocytes. Autopsy revealed generalized tuberculous adenitis. It was of interest that the monocytes were found only in association with the tuberculous foci in the lung and liver. The author suggested that the monocytic response might be due to a reactive irritation of the reticulo-endothelial system.

The following two case histories are reported as examples of a lymphocytic leukemoid response to miliary tuberculosis.

CASE REPORTS

CASE 1

R. O., a 59 year old white female, entered the Mt. Zion Hospital on January 5, 1945. She complained of generalized malaise and a swelling in the left side of her neck. Four months previously the patient had noted that she tired easily and had lost 10 pounds in weight in one month's time. Profuse perspiration at night caused her considerable discomfort. She was aware of dizziness upon sudden change of position. Just prior to entry it had been observed that she was febrile.

The patient stated that a nodular mass had been removed surgically from the left side of her neck at the age of 16. This consisted of one walnut-sized node surrounded by many smaller nodules. In 1938,
at the age of 53, the patient again entered the hospital because of the appearance of a mass in the left side of the neck which extended from the mastoid process to the angle of the mandible. The mass was firm in consistency, smooth in outline, and fixed to the underlying structures. Six exposures to roentgen ray did not alter its size, and it was surgically removed. The pathologist reported atypical tuberculosis, and acid-fast organisms were found in the stained sections. In January 1943, she saw her physician because serous fluid drained from the area of the wound in the left side of the neck where the nodes had been excised. With symptomatic treatment this sinus healed in two months. Nine months later she was seen again because of climacteric symptoms. At this time, the wound was healed and she had gained weight. She did not see her physician again until the present illness.

Physical examination revealed a well-nourished woman in no apparent distress. Blood pressure was 116/70 mm. Hg; pulse 88. There was a large, matted, movable mass in the region of the left submental triangle. Small nodes were palpable bilaterally in the anterior and posterior cervical chains. The heart was not enlarged and there were no cardiac murmurs. No abnormal findings were apparent on physical examination of the chest. The tip of the spleen was palpable 4 cm. below the left midcostal margin. The rest of the physical examination was essentially negative. No other adenopathy was noted.

Urinalysis revealed 1+ albumin, specific gravity of 1.019; no sediment abnormalities on microscopic examination. Blood examination showed hemoglobin of 8.9 Gm. or 58.4 per cent (Sahli); the red blood cell count was 3.02 million per cubic millimeter of blood; the white blood cell count was 6,100 per cubic millimeter of blood. The differential count showed lymphoblasts, 11 per cent; prolymphocytes, 64 per cent; lymphocytes, 24 per cent; granulocytes, 1 per cent. Almost all of the cells showed characteristics of young lymphocytes and lymphoblasts. The cytoplasm was deeply basophilic and contained a moderate number of azure granules. The chromatin was diffuse and between its meshes could be discerned several large nucleoli (figure 1). Differential counts done on four different occasions between January 6 and January 29, 1945, showed results similar to the first count.
In addition to symptomatic treatment, the patient received four blood transfusions over a period of two weeks with no subjective or objective improvement. The patient maintained a swinging daily temperature curve with peaks at 39.5°C. and 40.5°C. The fever followed no specific pattern, but for the most part was above 38°C. About February 4, 1945, she began to have periods of disorientation. On February 11, her respirations were labored and the patient became comatose and expired twenty-nine days after entry into the hospital.

Clinical diagnosis: Tuberculous adenitis; acute lymphocytic leukemia, aleukemic; myelophthisic anemia.

Necropsy

Gross Examination: The body was that of an obese white woman with generalized icterus. Multiple petechiae were present over the body and about both eyes. No palpable subcutaneous lymph nodes were noted. There was no excess free fluid in any of the body cavities. The organs were normally disposed.

The heart weighed 320 grams and was of usual contour and quite flabby. It was yellow tan, striated, and soft. The coronary ostia and the major coronary branches were patent.

The weight of the left lung was 650 grams; the right, 410 grams. The pleural surfaces were smooth, but on cutting were crepitant and dark red. The trachea and bronchi contained a moderate amount of frothy hemorrhagic material. The tracheobronchial lymph nodes were large, measuring up to 4 cm. They were grayish white when sectioned.

The liver weighed 1900 grams and was quite soft. The capsule was smooth, and on the cut surface the parenchyma was yellow and finely dotted with red. The gallbladder, pancreas, and adrenal glands showed no gross changes.

The gastrointestinal tract showed no gross changes. Near the cecum, there was a mass of translucent tissue resembling matted lymph nodes which measured 6 cm. in diameter. On section this was grayish white with yellow foci.

The spleen weighed 440 grams and was soft. On the cut surface it was dark red dotted with gray.

The combined weight of the kidneys was 380 grams. On cut surfaces they showed multiple hemorrhagic markings, but otherwise were not abnormal. The right ovary was replaced by a cystic mass filled with thick hemorrhagic material. Otherwise the pelvic organs were normal. There were no additional gross abnormalities of significance.

Microscopic Examination

Heart: The myofibrillae were thin with prominent striations and nuclei. The small vessel walls showed no changes.

Lungs: The alveoli were collapsed in large areas and the small vessels were distended. Elsewhere the alveoli and bronchioles contained granular eosinophilic material and a few polymorphonuclear cells.

Liver: The architecture was distorted by atrophy and the presence of broken-down cells in the central areas. There were many oval areas of necrotic tissue with an average diameter of one third of a lobe. These areas were scattered throughout the liver, and were composed of dense eosinophilic amorphous necrotic tissue in which a few ghosted nuclei were seen. There was a fine border of scattered lymphocytes about some of the nodules. Silver stain showed the usual reticulum network intact except in the caseous areas. Sections of liver stained by the Ziehl-Nielson technic revealed numerous clumps of acid-fast bacilli. No periportal lymphocytic infiltration was seen.

Spleen: The lymph follicles were quite small and sharply bounded by congested red pulp. Throughout the organ were necrotic foci of the same size as those observed in the liver and of similar appearance. Acid-fast organisms were noted in these caseous nodules also.

Lymph nodes: Sections of the lymph nodes from the cervical, tracheo-bronchial, preaortic, and mesenteric groups showed the same picture of numerous eosinophilic oval areas of necrosis. Again they were devoid of cells, blending peripherally with lymph node structures. These areas were devoid of reticulum by silver stain and contained myriads of acid-fast organisms.

Bone marrow: Spread diffusely throughout the marrow were numerous areas of necrosis which were devoid of any epithelioid reaction at their borders. The blood formative tissue was slightly hypoplastic. Megakaryocytes were rarely seen, but the plasma cells were slightly increased.

Miscellaneous: Sections of the adrenal gland, pancreas, parathyroid, thyroid, uterus, ovaries, kidney,
gallbladder, and urinary bladder showed no changes of significance. No changes were found in the brain or meninges.

Anatomic Diagnosis: Generalized tuberculosis of lymph nodes – (a) miliary tuberculosis, (b) hypoplasia of bone marrow; hemorrhagic cyst of ovary.

CASE 1

V. L., U130787, a 73 year old man, entered the University of California Hospital on August 19, 1946, complaining of dyspnea, orthopnea, and hemoptysis. The patient's history dated back to 1918 when he had his first episode of hemoptysis, which was treated with three weeks of bed rest. Again in 1919, he had an episode of severe hemoptysis and was told at that time that he had pulmonary tuberculosis. Otherwise the past history was noncontributory. In October, 1945, the patient had a swelling of the right ankle and lower leg, and a diagnosis of phlebitis was made. In February, 1946, he saw his physician because of generalized malaise. A white blood cell count at that time revealed a leukocytosis of 66,000 cells per cubic millimeter, with 95 per cent lymphocytes. There was no hepatosplenomegaly or adenopathy noted. He was given symptomatic therapy until June 18, 1946. At that time he was given Fowler's solution, 5 drops three times daily. However, the patient stopped the medication in five days because of nausea. The drug was again started and continued for the first two weeks of July. The white blood cell count averaged about 39,000 cells per cubic millimeter with 90 per cent lymphocytes at this time. During the two months preceding hospitalization, the patient had a cough productive of blood-tinged sputum. He also suffered from night sweats and fever.

On entry the patient was dyspneic and cyanotic. Blood pressure was 12.5 systolic and 70 diastolic. The temperature was 38.2 C.; the pulse, 110 per minute; the respirations, 30 per minute. On physical examination no adenopathy was noted. The trachea was deviated to the right and there was marked venous distention of the neck. The chest showed atrophy of the right shoulder girdle muscles. There was limited excursion of the right chest. There was flatness of the right upper third of the chest posteriorly and anteriorly to percussion. Crepitant rales were present over the entire chest with bronchial breathing over the right apex. No cardiac enlargement was noted. On deep inspiration the liver was palpable 7 cm. below the right midcostal margin; and the spleen, 3 cm. below the left midcostal margin. Bilateral pedal edema was present with brawny induration over the right ankle.

Laboratory Data

The urine showed faint albuminuria and had a specific gravity of 1.026. There were no abnormal findings in the sediment. Examination of the blood revealed hemoglobin of 9.5 grams, or 66 per cent (Sahli). The red blood cell count was 3.5 million per cubic millimeter; white blood cell count was 42,500 cells per cubic millimeter; the differential count showed prolymphocytes, 6 per cent; lymphocytes, 77 per cent; degenerative cells, 13 per cent; granulocytes, 4 per cent. An adequate number of platelets were present on blood films prepared with Wright's stain. The sputum contained large numbers of acid-fast organisms. The electrocardiogram showed an abnormal record suggesting coronary artery disease.

The patient was immediately digitalized with 8 cc. of "Cedilanid" intravenously and soon obtained marked relief from dyspnea. He was then given a maintenance dose of digitalis folia, 0.1 Gm. twice daily. The cyanosis receded slowly, but the patient continued to have a fever of between 38 and 39 C. at all times. A chest x-ray taken shortly after entry revealed extensive infiltration of the upper lobes bilaterally with marked pulmonary shrinkage on the right side displacing the mediastinal structures. A homogeneously distributed nodular peribronchial infiltration was present throughout both lungs. It was felt that the patient could receive convalescent care at home and he was discharged eleven days after entry. Before discharge he was given 500 cc. of citrated blood which was well tolerated. At time of discharge, his white blood cell count was 73,600 per cubic millimeter with 70 per cent lymphocytes and the red cell count was 4.12 million per cubic millimeter. A roentgenogram of the chest taken on the day of discharge showed a marked decrease in the transverse diameter of the heart from 13 cm. to 10.3 cm.

The patient was confined to bed at home. He was orthopneic and continued to have a productive cough and septic fever. He died September 14, 1946, seventeen days after discharge from the hospital.

Clinical diagnosis: miliary tuberculosis; far advanced pulmonary tuberculosis; lymphocytic leukemia; arteriosclerotic heart disease.
Necropsy

Gross examination revealed the body of an emaciated male. No lymph nodes were palpable. The right pleural cavity was obliterated because of adhesions. The trachea was deviated to the right and the lymph nodes of the mediastinum showed enlargement and pigmentation. The heart weighed 310 grams and the coronary vessels were patent throughout.

The right lung weighed 890 grams, the left 1010 grams. On the cut surface, they revealed marked fibrosis with grayish white infiltrations 1 to 3 mm. in diameter throughout the parenchyma. The right upper lobe revealed a small cavity 1 cm. in diameter.

The spleen weighed 300 grams. On section the corpuscles were well defined, but there were diffuse gray infiltrations throughout the pulp measuring up to 3 mm. in diameter.

The liver weighed 1390 grams and on section showed occasional whitish area, among the otherwise normal parenchyma. The kidneys were of normal size and architecture. Numerous pinhead gray areas were spread throughout the cortex. The same type of infiltration was noted in the sections of the adrenals.

The abdominal and mesenteric lymph nodes were enlarged. The bone marrow was pale but not remarkable otherwise. No other gross abnormal findings were noted.

Microscopic Examination

Lungs: The bronchi and bronchioles were dilated and showed peribronchial fibrous proliferation. An occasional conglomerate tubercle with central caseation and surrounding fibrous reaction was noted. Within a dilated vascular channel, a mass of tuberculous granulation tissue was seen and suggested a possible source of the miliary spread. In the alveoli surrounding the early conglomerate masses of tubercles, proliferating fibroblasts and epithelioid cells were seen. In addition to the older process, there was a widespread distribution of single or multiple young tubercules with little surrounding fibrous reaction.

Spleen: The parenchyma was largely replaced by tubercles showing minimal central necrosis and containing giant cells. In the scanty uninvolved areas, there was no obliteration of the sinusoids which contained many lymphocytes, large mononuclear cells, and a few red blood cells. A moderate epithelioid hyperplasia was noted. The rare germinal centers were distorted and replaced in part by young and old lymphocytes and many mononuclear cells.

Liver: The hepatic lobular pattern was well maintained. The sinusoids were distended but contained few cells. These were chiefly red blood cells. There were few lymphocytes, monocytes, or polymorphonuclear cells. Throughout the parenchyma young and old tubercules could be discerned. These contained giant cells and showed slight necrosis. Immediately adjacent to the tubercules, particularly in the periportal connective tissue, were large numbers of mature lymphocytes.

Kidneys: Several areas contained tubercles with central necrosis. Other areas showed large conglomerate portions of tissue with widespread caseation and a marked lymphocytic infiltration at the border. The intervening glomeruli and tubules appeared normal.

Lymph nodes: Bronchial and mesenteric nodes showed preservation of the normal architecture with a marked hyperplasia of the reticulo-endothelial pattern. The sinuses were intact and contained many lymphocytes and mononuclear and plasma cells. Tubercules were widely scattered among the intact lymphoid follicles. These were usually small without caseation, but showed marked giant cell formation. No capsular invasion nor abnormal number of mitoses was seen (figure 2).

Bone marrow: Several sections of sternal and vertebral marrow revealed extensive single and conglomerate tubercle formation with marked caseation and trabecular bone destruction. Aside from the tubercle formation there was a normal quantitative and qualitative relationship of the myelopoietic and erythropoietic series. Megakaryocytes were present in adequate numbers (figure 3).

Miscellaneous: Sections of the adrenals showed diffuse tubercle formation in the cortex and medulla with dense fibrous replacement. Studies of the thyroid, pancreas, gallbladder, testes, and prostate showed no changes of significance.

Anatomic diagnosis: (1) Bilateral pulmonary tuberculosis, fibrocaseous type, with cavity of right apex and diffuse right pleural adhesions. (2) Miliary tuberculosis of lungs (bilateral), liver, spleen, adrenals, lymph nodes, and bone marrow. (a) Reactive lymphoid hyperplasia of lymph nodes. (b) Lymphocytic leukemoid reaction of bone marrow. (3) Generalized arteriosclerosis with moderate coronary sclerosis and focal myocardial fibrosis.
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Fig 2.—Case 2, Lymph Node (X 120). Typical section of the diffuse tuberculous invasion. Diffuse hyperplasia with intact capsular wall present (lower right corner).

Fig. 3.—Case 2, Bone Marrow (X 120). The epithelial process is surrounded by marrow of normal architecture.
Both of these cases were diagnosed as lymphocytic leukemia when first seen by members of the Hematology Unit. It was not until necropsy that the question of a leukemoid response to tuberculosis arose. Krumbhar\textsuperscript{11} has stated that it may not be possible to distinguish between a terminal leukemoid blood picture and a true leukemia. Such was true in these case studies.

In Case 1, the miliary tubercles showed a fine necrotic matrix with no proliferation of fibrous tissue. The entire process consisted of massive necrosis and the diagnosis of miliary tuberculosis was made by demonstrating acid-fast organisms in these areas. These lesions were similar to those described by Leibowitz\textsuperscript{9} and Coley and Ewing.\textsuperscript{8}

The report by Leibowitz\textsuperscript{9} includes a review of the literature (especially European) of the necrotic lesions in tuberculous sepsis. One case reported by Marzullo and DeVeer\textsuperscript{4} revealed no epithelioid changes at autopsy, but rather necrosis. On entry to the hospital this patient had a white blood cell count of 57,000 with 15\% myeloblasts. He died of tuberculous pneumonia.

Rich and McCordock\textsuperscript{12} observed in animal experiments some correlation between the number of organisms and the extent of necrosis. The presence of extensive necrosis is probably correlated with the number of bacilli present. Upon reviewing their cases, these authors noted that acid-fast organisms were more numerous in the soft tubercles with extensive necrosis. In the more proliferative tubercle, the organisms were sparse. The soft tubercle is probably the result of a massive infection of the blood stream associated with a high degree of allergy.

Such a condition probably existed in Case 1. A long-standing tuberculous infection in the neck was associated with a miliary sepsis. Can we consider the lymphocytic leukemoid picture to be an agonal response to the infection? The interesting study of Wiseman and Doan\textsuperscript{13} may aid in understanding the lymphocytic response. These authors showed that the age of the lymphocyte can be determined by progressive variations in cellular cytology; namely, basophilia of the cytoplasm, chromatic density, and distribution of the non-segmented nucleus. They divided the circulatory lymphocytes into three classes—young, mature, and old cells. It was observed in rabbits that there was a marked increase in the percentage of young lymphocytes following infection by intravenous injection of avian tuberculosis bacilli. As the animal neared death from miliary tuberculosis, there was a sharp decline in the percentage of mature forms. Studies of clinical material also showed an increase in young lymphocytes with progression of pulmonary tuberculosis. The authors felt that the increase in young lymphocytes with tuberculosis infection indicated that these blood elements were utilized in the pathologic process.

From this study can we postulate that a marked stimulus of the tuberculotoxins shifted the response of the lymphocyte to the early stem forms. This might help explain the genesis of the lymphocytic leukemoid blood picture in the first case.

Case 2 presented a more controversial problem. In a patient of his age, with an illness of long duration and an elevated white blood cell count, the diagnosis of chronic lymphocytic leukemia was more tenable. It was believed when this patient was first studied that a chronic leukemia had activated an old fibrotic tuberculosis
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and that this was associated then with a diffuse hematogenous peribronchial extension culminating in cardiac embarrassment from a subacute cor pulmonale. The tender hepatomegaly and splenomegaly were first noted when the patient entered the hospital with cardiac embarrassment. This patient had been observed by a staff hematologist regularly for five months before entry, and at no time did he note adenopathy or hepatosplenomegaly.

Rossle\textsuperscript{4} has observed patients with lymphocytic leukemia without adenopathy or hepatosplenomegaly. However, microscopic examination of the bone marrow in these cases revealed leukemic infiltration. In the second of our cases, necropsy findings of young and old tubercles throughout the organs and lymph nodes suggest a repeated bacteremia. Can we postulate that this patient had a persistent leukemoid reaction for six months before death? In a study of leukemoid reactions, Hill and Duncan\textsuperscript{13} recently reported a case of leukemoid reaction which existed over a three year period in a 40 year old Negro male who had been followed in a leucotic clinic. The white blood cell count varied from 23,000 to 78,400 per cubic millimeter of blood, and of these, 3 per cent were myeloblasts and 25 per cent myelocytes. Autopsy revealed a suppurative osteomyelitis of the sacrum associated with a gangrenous, necrotic abscess of the right thigh and an abscess of the right posterior lung field. In a similar manner, a persistent lymphocytosis might allow us to explain the blood findings in this case as a result of persistent irritation of the lymphoid tissue and marrow. Feldman and Stasney\textsuperscript{16} have suggested an allergic response of the bone marrow to explain the myelocytic leukemoid blood response in tuberculous rabbits receiving tuberculin injections. We know of no experimental work showing lymphatic leukemoid response to tuberculin to indicate that lymphocytosis to the extent observed in these patients may be an allergic response to miliary tuberculosis. However, the lack of any evidence on microscopic examination of leukemic infiltration in the tissues in Case 2 forced us to conclude that the elevated white blood cell count of mature lymphocytes was the response to a progressive miliary tuberculosis.

Muller\textsuperscript{1} has commented on the rarity of the leukemoid reaction. During a five year period in which approximately 2000 patients with tuberculosis were observed, no leukemoid blood pictures were seen. In rare cases, a few myelocytes were seen, and no case showed over 3 per cent myelocytes.

**Summary**

Two cases of miliary tuberculosis that were diagnosed clinically as lymphocytic leukemia are presented. Both cases had evidence of chronic tuberculosis which was of 43 years' duration in Case 1 and of 28 years' duration in Case 2. Both patients had granulocytopenia and anemia.

Autopsy findings revealed no evidence of leukemic infiltration, but a diffuse miliary tuberculosis, involving all of the hematopoietic tissues, existed in both cases.

**REFERENCES**

\textsuperscript{1} Muller, G. L.: Clinical Significance of the Blood in Tuberculosis. New York, The Commonwealth Fund, 1943.
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