

THE LEUKEMIAS

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Leukemia is a fairly common blood dyscrasia characterized by unrestrained overgrowth of tissues which normally form leukocytes, as well as by areas of leukopoietic proliferation in other parts of the body. There is much to indicate that it is a neoplastic disease. Although the length of life of patients with leukemia varies greatly, the disease always ends fatally. Different types of leukemia may present such widely varying clinical pictures that many diseases are suggested.

During the past thirteen years 357 patients with leukemia have been studied in the Cleveland Clinic. Detailed blood studies in all cases were made in the hematology laboratory, and bone marrow preparations were studied when indicated. When a blood examination shows a definite leukemia, a bone marrow film only confirms the diagnosis; but when the diagnosis from the blood examination is difficult because of leukopenia or a scarcity of immature cells, the marrow findings may be diagnostic. All blood and marrow preparations are kept in a permanent file for review.

INCIDENCE

The exact distribution of the 357 cases according to the five types of leukemia is as follows: monocytic 52, acute myeloid 60, chronic myeloid 90, acute lymphoid 54, chronic lymphoid 101.

I analyzed in detail 250 of the 357 case histories, or 50 consecutive cases of each of the five types. In this survey almost all the monocytic, the acute myeloid, and the acute lymphoid cases were included. Consecutive cases of chronic myeloid and chronic lymphoid leukemia were taken to insure a fair sample.

Men are more susceptible to the disease than women. In the 250 cases the proportion is almost 2 to 1 (62.8 per cent to 37.2 per cent). Every age is represented.

Every decade is included in the monocytic group. One infant with monocytic leukemia was only $3\frac{1}{2}$ months old when the diagnosis was made, and several patients were 70 or over. The chronic lymphoid type is most common between 50 and 70; no patients were under 20, and only 2 patients were under 40. However, 80 per cent of the cases of acute lymphoid leukemia occurred under the age of 20. Chronic myeloid leukemia occurs most frequently between 40 and 60. In this series, however, all decades were represented. One child $2\frac{1}{2}$ years of age had typical chronic myeloid leukemia. The acute myeloid cases were evenly distributed in all decades.

DIAGNOSIS

All types of leukemia present two fundamental characteristics, toxemia and infiltration. The signs and symptoms may be due to a combination of the two processes or entirely to one or the other.

The more important symptoms of toxemia are fever, loss of weight, sweating, anorexia, malaise, and joint pain and swelling. The exhaustion common to all types of leukemia is due partly to toxemia and partly to anemia. In most cases the anemia seems to be the result of overcrowding of the marrow spaces by leukopoietic overgrowth, preventing normal red cell formation. However, toxemia, because of its depressing effect on the bone marrow, is often a factor in the anemia. Especially in acute cases the marrow may be even aplastic although immature, making the differentiation of primary aplastic anemia and leukemia most difficult. The aplasia can be explained only on the basis of a toxic effect on the bone marrow.

Hyperplasia and infiltration of tissues and organs everywhere in the body are always present in leukemia. The enlarged spleen and lymph glands represent an increase in the size of normal organs and tissues through overgrowth of white cell-forming tissues. The bone marrow is usually hypertrophied. The marrow which normally forms leukocytes is overcrowded. The part of the marrow which normally shows little activity—as in the long bones—also becomes hyperplastic and overgrown with leukocytes of different types. White cells may multiply anywhere in the body either by metaplasia or by localization through the blood stream and subsequent multiplication.

Other important fundamental changes which depend on toxemia and infiltration of tissues are anemia, hemorrhage, and infection.

The almost constant occurrence of anemia from toxic depression of bone marrow activity, crowding out of erythrogenic tissue by overgrowth of white cells, or a combination of these factors has already been mentioned. Hemoglobin as high as 80 per cent was found in only 24 of the 250 patients, and only 3 patients had acute leukemia without anemia. Most patients without anemia had chronic lymphoid leukemia. The anemia is the cause of weakness and shortness of breath complained of by many patients as well as pallor.

Hemorrhage is frequent in all types of leukemia and may occur in any part of the body. In some patients the tendency to abnormal bleeding is due to platelet deficiency, in others to increased permeability of the vessels without thrombopenia, and in still others to a combination of these two factors. Abnormal bleeding is commonly manifested as petechiae, especially in acute leukemia. Gross bleeding in the brain or from the intestinal tract is not uncommon. Cerebral hemorrhage is a

frequent cause of death in chronic myeloid leukemia in which the number of platelets is usually increased. Hemorrhage may be difficult to control even by transfusion.

Increased susceptibility to infection is prominent. This occurs most frequently in acute leukemia in which leukopenia is common and mature polymorphonuclear cells in blood and tissue are greatly reduced. In the absence of normal defense cells, resistance to bacterial infection is very low. Common sites of infection are around the teeth and gums and in the tonsils and rectum. Infection may be a factor in the fever usually present.

Because leukemia is a disease of the blood-forming organs, the diagnosis must finally be based on changes in the circulating blood and in the bone marrow. Anemia is an almost constant finding, and it is usually marked in every acute or serious case of leukemia. The patient who does not have an anemia has either mild chronic lymphoid leukemia or early chronic myeloid leukemia. The anemia may be of any type, but a marked microcytic or hypochromic anemia is seldom encountered unless blood loss has been severe. In many cases the anemia is definitely macrocytic, especially in the patient with leukopenia, and pernicious anemia may be suspected. The macrocytosis of leukemia is not adequately explained. An increased volume of red cells is believed to indicate a deficiency in supply or a lack of use of the erythrocyte-maturing factor present in liver extract. In leukemia the supply of the specific maturing factor is evidently adequate, since the anemia is not improved by treatment with the specific maturing principle. The disease probably interferes with utilization of the specific substance in the bone marrow.

A number of cases of hemolytic anemia were encountered, several of which were spherocytic, suggesting congenital spherocytosis. In one case the spleen was removed before leukemia was recognized.

The platelets are extremely variable, but in acute leukemia are often so low that thrombopenic bleeding occurs. In about 10 per cent of these cases abnormal bleeding, usually due to thrombopenia, was the most important symptom. The thrombopenia may be due to crowding out of the megalokaryocytes in the marrow or to depression of marrow function by toxemia.

Study of the white cell is the most important part of the blood examination; in the last analysis the diagnosis of leukemia must rest on abnormalities in the leukocytes. Leukocytosis is always associated with leukemia and is often considered necessary for the diagnosis, but the type of leukocytosis is extremely variable. Of these 250 cases the white cell count on admission was below 6000 per cu. mm. in 27.6 per cent, from 6000 to 10,000 in 6.8 per cent, and over 10,000 in only 65.6 per cent of the patients. Thus, leukocytosis was present in only two-thirds of the

patients. The white cell count for the 357 patients was much the same; in 32.2 per cent the white cell count was under 10,000 per cu. mm., and in 67.8 per cent over 10,000. In many cases of leukocytosis the count was not very high, although occasionally a very high count was found. One patient with chronic lymphoid leukemia had a count of over 2,000,000 white cells on numerous occasions, and at times this patient's white cell count was higher than the red cell count. Many seriously ill patients never had a white cell count above 1000. In all cases with leukopenia, however, the bone marrow is immature and usually hyperplastic. For this reason patients are said to have leukopenic leukemia rather than aleukemic leukemia.

Usually the differential count of leukocytes reveals immature cells. In myeloid leukemias these may be the intermediate series: myelocytes, promyelocytes, metamyelocytes, and myeloblasts. Intermediate cells may be seen in various conditions, but myeloblasts, monoblasts, and lymphoblasts are probably seen only in myeloid leukemia.

Often not enough white cells are available for study to find many immature cells. Here concentrated preparations of leukocytes are of the greatest value. These are simply prepared by allowing the red cells to settle out by gravity for a short time, centrifuging quickly, and making films from the buffy coat, or layer of white cells on the surface of the red cells. In this way any number of white cells can be obtained for microscopic study, and blasts and immature cells are easily found.

The cells in the circulating blood, however, only reflect the activity of the bone marrow in which the leukocytes are formed. A biopsy of bone marrow may be obtained by trephining the sternum or some other bone. In most cases an entirely satisfactory specimen of the marrow may be obtained by aspirating the sternal marrow with a large needle and making coverslip preparations with the material obtained. When the diagnosis of leukemia is difficult, it may be confirmed by examination of the marrow; in all doubtful cases study of the bone marrow is mandatory.

CLINICAL FEATURES

The clinical features of different types of leukemia are of primary interest. In all types the complaints vary widely. Anemia and weakness were the outstanding features of the clinical picture in patients with **monocytic leukemia**. Fever alone or with anemia was prominent and was often associated with generalized body aching. Two other prominent symptoms are infection and abnormal bleeding. The infection most often involves the buccal tissues, so that the diagnosis can often be made from the condition of the gums and other tissues of the oral cavity alone. Hypertrophy of the gums is especially characteristic and may progress

very rapidly, usually with necrosis. The necrosis may become chronic and persist for months. Other patients, equally typical of monocytic leukemia insofar as the hematologic diagnosis is concerned, may never show infection of any kind. Abnormal bleeding may be very severe and difficult to control. It is most likely to occur in patients with evident toxemia as manifested by fever and anemia and may progress rapidly. Bleeding here is usually the result of thrombopenia.

The clinical picture of monocytic leukemia varies more than that of any other type. One patient was admitted recently to the dermatological service with multiple skin ulcerations previously diagnosed and treated as furunculosis. The patient had a persistent fever. Until the blood examination leukemia was not suspected. The blood examination showed 20,000 leukocytes with many monocytes and monoblasts. Severe anemia was also present. Sternal puncture revealed hyperplastic marrow with a great excess of monocytes. Biopsy of a local lesion confirmed the diagnosis of monocytic leukemia. Another patient who had only a marked anemia during the course of his disease lived several years with multiple transfusions. There was no leukocytosis, although a high proportion of the cells were monocytes. The anemia was always macrocytic. Many other equally unusual clinical histories could be detailed. The youngest patient I have seen with leukemia was $3\frac{1}{2}$ months old and had the monocytic variety. One-half the patients in this group were over 45 years of age.

The leukocyte count in monocytic leukemia is seldom high. Sixty per cent of this group never had a count above 10,000. Only 3 patients had a count over 100,000. The anemia was macrocytic in almost one-half the cases in which the volume index was measured. The spleen and glands were seldom enlarged. In some cases blasts were never seen.

Acute leukemia runs a more rapid course and is characterized by the presence of more immature cells in the blood and marrow.

Acute lymphoid leukemia occurs principally in children; the disease is rare in older persons. Two-thirds of the patients in this group were under 10 years of age. I have been impressed with the frequency of occurrence of skeletal pains in acute lymphoid leukemia. Several patients had definite arthritis. One boy of 7 had marked swelling of an ankle and intense pain in the legs. Involvement of most of the large joints confined him to bed for two months before admission. The arthritis was associated with fever and anemia.

The outstanding characteristics of the acute lymphoid type are anemia and weakness and an abnormal tendency to bleeding, usually manifested by easy bruising. The spleen was enlarged in most cases. The patients complained of enlarged glands, but the enlargement was mini-

mal. Perhaps this group follows the textbook description more closely than any of the other groups. When a child presents fever, anemia, easy bruising, and enlarged glands and spleen, the diagnosis is usually acute lymphoid leukemia. Here again leukopenia is common, although very high counts are also observed. Anemia is always present and usually severe. The anemia is seldom macrocytic, often microcytic.

Acute myeloid leukemia has much in common with the acute lymphoid type. The patients in this group were older. All decades from the first to the seventh were represented, but only 6 patients were under 10. The other cases were quite uniformly distributed over the 10-70 interval. The presenting complaints were perhaps the most varied of all groups. Among these were chills and fever, enlarged spleen, swelling of the face, stomach trouble, sore throat, weakness, pernicious anemia, joint pain and swelling, loss of appetite, and fever. Actual joint involvement is much less common than in the acute lymphoid type. The outstanding clinical features are anemia and fever. Abnormal bleeding may be prominent but is infrequent. Infection is not so common as in the monocytic group. Necrosis occurs but is uncommon. The leukocyte count is seldom high. Two-thirds of the group of 50 patients had a leukocyte count under 10,000. In 3 cases no myeloblasts could be found in the blood, although the marrow showed the typical picture of acute myeloblastic leukemia. Less than half the patients had a palpable spleen. At times there was some general glandular enlargement.

In many instances **chronic lymphoid leukemia** is benign and has a prolonged course, although, as always, the disease ends fatally. It is a disease of older persons. I have never seen this type in a younger person. Eighty-eight per cent of the 50 patients in this group were over 50 years of age; only 3 were under 45. Often no blast cells were seen. Usually fragile cells or smudges were present and probably represented immaturity. Even in the mild chronic cases the bone marrow showed a high proportion of hybrid cells. Usually the total leukocyte count was high. Only one patient had a count less than 10,000. Many patients had no anemia. This is the only type of leukemia which persists for any length of time without development of anemia.

The clinical symptoms of chronic lymphoid leukemia also are often mild. Enlarged glands and spleen may be the only abnormality for a long time. Most patients who have had leukemia for any length of time belong in the chronic lymphoid group. This type not infrequently has been an incidental finding in the examination of patients. Patients entering the Clinic for chronic cough, iritis, abdominal pain, rheumatism, pain in the legs, headache, leukocytosis, bladder trouble, constipation, and "sick spells" have had chronic lymphoid leukemia. In most

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cases the outstanding clinical feature was enlarged glands or spleen. Weakness was relatively uncommon. Infection as a complication was seldom encountered.

Chronic myeloid leukemia is characterized principally by weakness. This is partly due to anemia, which is almost always present, but the toxemic character of the disease is also an important causal factor in the exhaustion. Many patients were concerned about the enlarged abdomen resulting from a marked splenomegaly. Fever, which is very frequent, was the presenting complaint in several instances. One patient was confined to a tuberculosis sanatorium for months because an acid-fast infection was suspected when the fever was really due to leukemia. The tendency to bleed is greater in the chronic myeloid than in the chronic lymphoid type, probably because of the more severe toxemia. Here the abnormal hemorrhage is not due to thrombopenia but to the toxic effect of the disease on the endothelium of blood vessels. Usually the platelet count is high. Not infrequently hemorrhage is the cause of death. Infection is uncommon. In this group the patients' ages varied from $2\frac{1}{2}$ to 76 years. Most patients were in the middle age group. Usually the total leukocyte count is high. In only three instances was it less than 10,000, and in over half the patients the count was above 100,000. Blasts were almost always found.

SUMMARY

Leukemia is a generalized disease and may affect any part of the body. It is characterized primarily by toxemia and cellular infiltration of organs and other body tissues.

The youngest patient in this series of 357 cases was $3\frac{1}{2}$ months old and the oldest 76 years. Monocytic leukemia and acute myeloid leukemia affect persons of all ages. Acute lymphoid leukemia is most common in childhood, while chronic lymphoid leukemia and chronic myeloid leukemia are predominantly diseases of middle age.

The greatest variety of clinical pictures is encountered, so that there is little that is characteristic of the disease. The signs and symptoms are largely the result of anemia, hemorrhage, and infection due to toxemia and cellular infiltration. The bone marrow is always involved. It is usually hyperplastic but may be aplastic although immature.

Leukocytosis is often absent, especially in the acute types. In the entire group of cases the leukocyte count was below 10,000 in one-third of the patients. In 100 patients with acute lymphoid or acute myeloid leukemia the count was below 10,000 in over one-half of the patients.

Oral infection with hypertrophy of the gums is a prominent symptom in monocytic leukemia. The spleen is seldom palpable. The leukocyte count is usually not very high. The anemia is often macrocytic.

Acute lymphoid leukemia is characteristically a disease of childhood. Anemia, bleeding, and joint pain and swelling are frequent symptoms.

Acute myeloid leukemia occurs in all ages and is characterized by the greatest variety of symptoms and clinical findings.

Chronic lymphoid leukemia is often a very mild disease and runs a benign course. Enlargement of glands and spleen is the outstanding feature.

Chronic myeloid leukemia is characterized by marked toxemia causing almost constant fever and anemia.

INTRAMEDULLARY FIXATION OF CERTAIN FRACTURES OF BOTH BONES OF FOREARM

Report of Two Cases

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Everyone who has treated many fractures in the middle third of both bones of the forearm realizes the difficulty of reducing and maintaining these fractures in proper position. Even in skilled hands several manipulations may have to be carried out before a satisfactory and acceptable position can be obtained in both bones.

The use of the Kirschner wire through the lower end of the radius and the upper end of the ulna to maintain traction is attended with certain difficulties and the possibility of pin infection. Internal fixation by means of a metal plate is also a difficult procedure, particularly in children because the bones are quite small and do not lend themselves to plating.

Intramedullary use of the Kirschner wire in fractures of the clavicle has been reported on many occasions with excellent results, and it has been suggested that intramedullary use of the Kirschner wire might prove effective in fractures of both bones of the forearm. However, I cannot find any article in the literature in which this method has been previously employed for this type of fracture. In cases in which open operation was indicated in order to procure a satisfactory reduction, I found the use of intermedullary fixation so simple in application and so gratifying in result that I wish to report two cases.