

Myeloblastic Leukemia Preceded by Prolonged Hematologic Disorder

By MARJORIE J. WILLIAMS

INFORMATION REGARDING THE ONSET of myeloblastic leukemia is meager. It appears probable that in the majority of cases the onset is sudden as medical advice is rarely sought before the development of the classical picture. In a few cases, however, there is a relatively prolonged period of non-leukemic blood dyscrasia preceding acute leukemia.¹⁻¹⁰ The significance of the preliminary disturbance has not been fully evaluated at this time for it is not known whether it is an intrinsic part of the subsequent leukemia or whether the latter constitutes a coincidental sequel. It would appear that study of this preliminary disease period might be enlightening but, currently, its unequivocal recognition prior to the development of leukemia does not seem possible. However, since many of the recorded cases of this type bear a close similarity to one another, a tentative diagnosis might be hazarded prior to the development of leukemia. Investigative procedures could then be initiated.

The preliminary phase is usually characterized by a deficiency in the peripheral blood of one or more elements of marrow hemopoiesis, resulting in anemia, neutropenia, thrombocytopenia, or combinations thereof. At the same time, the marrow is moderately hyperplastic and may or may not show a maturation arrest in the granulocytic series.⁷ Not infrequently the anemia is hemolytic although it is not consistently accompanied by an elevated reticulocyte count.⁹ Rarely acute myeloblastic leukemia may be preceded by polycythemia vera,¹⁰ by myelofibrosis with myeloid metaplasia,⁸ or by erythremic myelosis.¹¹

As greater familiarity with this type of case is a necessary preliminary to further investigation, it seems desirable to record a case in which acute myeloblastic leukemia developed following a nine-year period of blood disorder.

CASE REPORT

The subject was a Latin-American, born in Texas, September 9, 1903. Prior to induction into the army in 1942, he had worked as a laborer. While in the army he was assigned to an antiaircraft unit. There were no significant items in either his personal or his family history. At no time was he exposed to known bone marrow toxins.

As the course of the disease was long and complex, it will be considered in four sections.

Initial Phase

In May 1944, while serving with the army in Italy, he noted fatigue, jaundice and slight bleeding from the gums. Hematologic studies revealed anemia, leukopenia and thrombocytopenia with prolonged bleeding and clotting times (table 1). Aspirated sternal marrow was reported to be hypoplastic with lymphocytes constituting 80 per cent of the nucleated cells. Several blood transfusions were given, and the patient was sent back to the United States.

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TABLE 1.—Peripheral Blood Studies

| Phase | Date | RBC mill. per cu.mm. | Hemo- globin (Gm.) | Hema- tocrit | WBC per cu.mm. | Neutro- phils per cent | Myelo- cytes per cent | Blast cells per cent | Platelets per cu.mm. |
|-----------|------------|----------------------------|--------------------------|-----------------|----------------------|------------------------------|-----------------------------|----------------------------|-------------------------|
| Initial | May 1944 | 1.31 | 4.8 | 14 | 1,950 | not done | not done | not done | 50,000 |
| | Aug. 1944 | 2.56 | 7.7 | not done | 2,850 | not done | not done | not done | 60,000 |
| Remission | March 1946 | 4.70 | 14.0 | not done | 3,500 | not done | not done | not done | not done |
| Relapse | Nov. 1950 | 2.99 | 11.5 | 38 | 3,000 | 30 | 0 | 0 | 128,000 |
| | July 1951 | 2.07 | 6.0 | 24 | 1,700 | 9 | 0 | 0 | 84,000 |
| | Jan. 1952 | 1.22 | 4.0 | 15 | 2,300 | 15 | 0 | 0 | 36,000 |
| | Aug. 1952 | 1.23 | 4.0 | 15 | 3,150 | 14 | 2 | 0 | 170,000 |
| Leukemic | Nov. 1952* | 4.29 | 13.5 | 44 | 10,200 | 35 | 2 | 18 | 238,000 |
| | Dec. 1952 | 2.62 | 8.5 | 30 | 48,000 | 20 | 6 | 35 | 536,000 |

* Anemia alleviated by blood transfusions.

TABLE 2.—Percentage Distribution of Nucleated Cells in Aspirated Marrow

| Date | Myelo- blasts | Promye- locytes | Myelo- cytes | Meta- myelo- cytes | Seg- mented granu- locytes | Lym- pho- cytes | Mono- cytes | Mega- karyo- cytes | Pro- normo- blasts | Normo- blasts | Total |
|---------------|------------------|--------------------|-----------------|--------------------------|-------------------------------------|-----------------------|----------------|--------------------------|--------------------------|------------------|-------|
| Sept. 1944... | — | 1.5 | 6.5 | 35.0 | 6.0 | 34.0 | 1.0 | 1.0 | 2.0 | 13.0 | 100.0 |
| July 1945.... | 8.0 | 4.5 | 3.5 | 43.0 | 4.5 | 6.0 | — | — | 7.5 | 23.0 | 100.0 |
| Dec. 1950... | 2.0 | 2.0 | 10.0 | 15.0 | 4.0 | 19.0 | 3.0 | — | 4.0 | 41.0 | 100.0 |
| Sept. 1951... | 8.2 | 5.8 | 3.7 | 4.4 | 4.4 | 1.8 | 2.5 | 0.7 | 25.2 | 43.3 | 100.0 |
| Sept. 1952... | 4.6 | 1.6 | 4.1 | 11.4 | 9.7 | 2.7 | 8.7 | — | 8.5 | 48.7 | 100.0 |
| Nov. 1952... | 17.8 | 5.4 | 6.1 | 10.2 | 12.7 | 9.6 | 16.2 | — | 2.4 | 19.6 | 100.0 |

In August 1944 he entered an army hospital in the United States. On admission, it was noted that he was jaundiced, had petechiae on his chest and was bleeding slightly from the gums. The liver and the spleen were not palpable. Blood studies showed persistence of the pancytopenia (table 1). The bleeding time was 22 minutes; prothrombin time, 90 seconds (control 21 seconds), and there was no clot retraction after 24 hours. From August 1944 until April 1945, he remained continuously in hospital. In September, bone marrow was aspirated and showed hypoplasia with relative lymphocytosis; toxic granulation of the mature polymorphonuclear leukocytes was observed (table 2). It was reported that there was no evidence of leukemia. During this eight month period, he received about 40 blood transfusions. His general and hematologic condition gradually improved and, early in 1945, it was observed that transfusions were required less and less frequently. During this entire period of hospitalization, he was given ferrous sulfate and cobalt sulfate and, from January to April, this was supplemented by liver extract.

From April 1945 until March 1946, he was followed as an outpatient, and during the earlier part of this period, he received occasional blood transfusions. In July, aspirated sternal marrow was reported to be within normal limits (table 2). As he had been taking atabrine prophylactically at the onset of his illness, he was given a course of the drug to determine whether bone marrow depression would occur; no evidence of marrow change was observed. His blood was tested for equine infectious anemia¹² with a negative result. In March 1946, at the time of discharge from hospital, the peripheral blood was considered to be within the normal range.

Period of Remission

From March 1946 until November 1950, he was followed by a Veterans Administration Regional Office. Once a year during this period, he was examined and blood counts were performed. He remained in essentially normal condition until the fall of 1950 when he noted progressive fatigue and pallor. Hematologic studies at the Regional Office revealed severe anemia.

Period of Relapse

In November 1950, he was admitted to the Veterans Administration Center, Temple, Texas. He was complaining of weakness and giddiness with cramps in the hands and legs. Physical examination showed marked pallor and slight enlargement and tenderness of the liver. The spleen was not palpable and there were no enlarged lymph nodes.

Admission laboratory studies showed a macrocytic anemia with neutropenia and thrombocytopenia and a normal reticulocyte count (table 1). The serum bilirubin was slightly elevated (1.51 mg. per cent). The bleeding and clotting times were normal.

Sternal marrow aspirated in December 1950 showed slight normoblastic hyperplasia with a tendency toward maturation arrest in the granulocytic series at the metamyelocyte level (table 2). A marrow biopsy was then performed and histologic study demonstrated focal hyperplasia of the erythroid series superimposed on normal cellularity. Moderate siderosis was present (fig. 1). As a result of these investigations, the patient was tentatively classified as a case of refractory anemia with a slightly hyperplastic marrow.

From December 1950 until September 1952, the patient's condition remained essentially unchanged. He received about 50 blood transfusions, which maintained his hemoglobin at about 8.0 Gm. per cent. Courses of both cortisone and ACTH failed to improve his condition. In September 1951 sternal marrow was again aspirated and was found to be hypercellular with marked hyperplasia of the erythrocytic series particularly at the pronormoblast level (table 2). Granulopoiesis was scanty with slight maturation arrest at the myeloblast and promyelocyte levels; occasional giant metamyelocytes were seen. There was no evidence of leukemia (fig. 2). In view of the erythropoietic changes, it was decided to embark upon a course of folic acid and crude liver extract. This proved to be ineffectual.

In September 1952, aspirated sternal marrow showed hypercellularity with erythropoietic hyperplasia at the normoblastic level (table 2). There was no evidence of leukemia. It was considered that a hemolytic anemia was unlikely in view of the following studies: reticulocyte count 1.4 per cent; Coombs test negative; osmotic fragility of red blood cells normal; serum bilirubin 0.7 mg. per cent. A series of fresh blood transfusions was embarked upon and he received three or four such transfusions each week for a period of two months (September

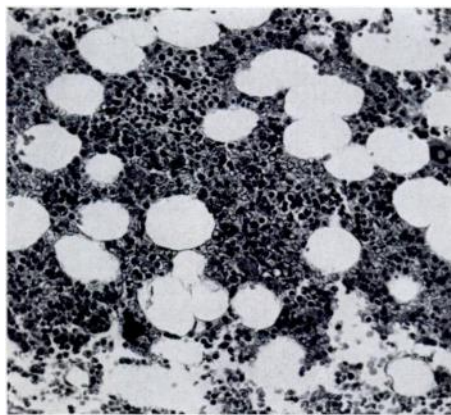


FIG. 1.—Sternal marrow, Dec. 1950, showing minimal hypercellularity. $\times 93$.

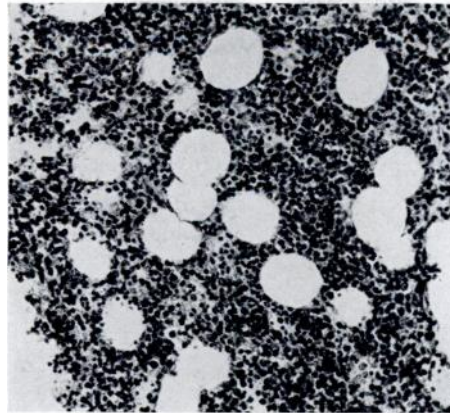


FIG. 2.—Sternal marrow, Sept. 1951. Note increase in cellularity. $\times 93$.

and October). Early in the course of intensive transfusion therapy, it was noted that a few normoblasts and myelocytes were appearing consistently in the peripheral blood and that there was a slight monocytosis (10 per cent). The anemia was unchanged but the neutropenia and thrombocytopenia were less severe. At the end of October, the patient began to complain of abdominal pain and, for the first time in the entire illness, the spleen became palpable.

Leukemic Phase

During November 1952, the spleen became progressively larger and was persistently tender. It was found that the white blood count had risen to 10,200 per cu. mm. with 18 per cent myeloblasts and 2 per cent myelocytes; 5 normoblasts per 100 leukocytes were present (table 1). Sternal marrow at this time was highly cellular with granulopoiesis predominating over erythropoiesis and accompanied by a slight monocytosis (table 2). Myeloblasts and promyelocytes constituted 23.2 per cent of the nucleated cells. A diagnosis of acute myeloblastic leukemia was made.

From then on the course was downhill with progressive deterioration in general condition. The white blood cell count rose gradually to 48,000 per cu. mm. with 35 per cent blast forms.

The patient expired on January 11, 1953 and an autopsy was performed.

Autopsy Findings

External examination showed a small slightly emaciated male with abdominal distention. There were no petechiae in the skin. The superficial lymph nodes were not enlarged.

The peritoneal cavity contained about 1500 ml. of clear yellowish fluid.

The liver weighed 2500 Gm. and the parenchyma was orange-tan in color. No other gross changes were observed.

The spleen weighed 2750 Gm. Its capsule was thickened and roughened. Sectioning the organ revealed multiple red to yellow firm infarcts situated predominately beneath the capsule. The viable pulp was a dark plum color and was swollen and soft (fig. 4).

The pancreas weighed 50 Gm. and was of an orange hue.

The mediastinal, para-aortic, peripancreatic and porta hepatic nodes were all moderately enlarged, of soft consistency and orange-brown in color.

Examination of the bone marrow of the sternum, multiple ribs, the lumbar vertebral bodies and of the right femur revealed it to be a golden brown color and of a soft pasty consistency.

No other significant gross findings were observed.

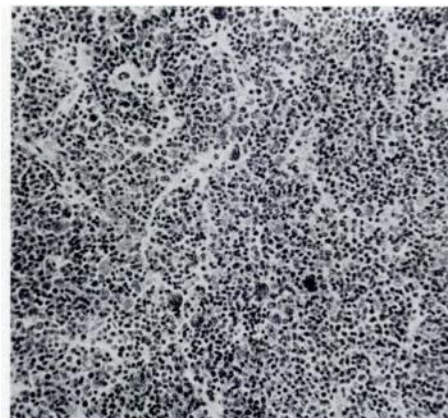


FIG. 3.—Bone marrow at autopsy showing loss of architecture with marked cellularity. $\times 93$.



FIG. 4.—Longitudinal section of spleen demonstrating both infarcts and enlargement of the organ.

Microscopic Study

In the liver, macrophages containing brown granular pigment were seen at the portal triads. Similar pigmented material was present in many of the Kupfer cells. Collections of immature cells, identified as myeloblasts, lay in many of the sinusoids. Cirrhosis was not present.

In the pancreas, there was moderate interstitial fibrosis. Brown pigment was present in many of the cells of the pancreatic acini and in macrophages in the interstitial tissue.

The normal splenic architecture was entirely lost, and was replaced by a delicate mesh of fibrous tissue intimately intermingled with swollen reticulum cells. There was widespread myeloblastic infiltration, the cells occurring singly and in clumps. Many recent infarcts were present and, at the junctions of these with viable tissue, there was heavy granulocytic infiltration. At the margins of the infarcts the vessels were plugged with myeloblastic cells.

The lymph nodes all showed a similar microscopic picture. The basic architecture was retained. The sinuses were tremendously distended by myeloblasts mixed with a lesser number of macrophages containing brownish pigment.

The bone marrow, at all sites examined, showed replacement of the normal tissue by sheets of tightly packed myeloblasts (fig. 3). In a few areas, foci of erythropoiesis with megakaryocytes could still be identified. Brown pigment, both in macrophages and lying free, was conspicuous.

The brown pigment, present in the liver, the pancreas, the spleen, the bone marrow and the lymph nodes, was demonstrated histochemically to contain iron.

Autopsy Diagnosis

The autopsy diagnosis revealed myeloblastic leukemia, recent splenic infarcts, hemosiderosis.

COMMENT

This case illustrates that acute leukemia may be preceded by a prolonged period of hematologic disorder, which may be punctuated by a period of remission. In view of the fact that the preliminary disturbance merged into the terminal leukemia, it is hard to believe that the latter was coincidental. However this possibility cannot be entirely excluded. It is believed that both the panmyelopathic disease and the myeloblastic leukemia were both manifestations of derangement of the mechanisms controlling maturation and release of cells from the marrow. The terminal leukemia may represent a final collapse of these controls with resultant uninhibited proliferation and release of primitive cells.

The various authors, who have studied cases of this type, have felt that the initial blood dyscrasia bore some relation to the subsequent leukemia.¹⁻¹¹ Adams, recognizing both aplastic anemia and leukemia as disorders of cell growth, believes that they may follow one another as manifestations of the same disease.⁶ Collins and Ross studied a case in which the onset of acute leukemia was preceded by a macrocytic anemia with neutropenia and thrombocytopenia associated with a megaloblastic marrow.⁴ These authors expressed the opinion that the anemia preceding or associated with myeloblastic leukemia is the outcome of an unknown stimulus affecting both the erythrocytic and granulocytic marrow tissue either simultaneously or successively. A somewhat similar case has been described by Foy and his associates.² They suggest that in cases in which a megaloblastic anemia antedates or is associated with acute leukemia (cases of so-called leukanemia), there may be a maturation defect at the hematocytoblast level due to deficiency of one or more essential factors. Whitby has also speculated that leukemia may prove to be a deficiency disease manifested by derangement of the factors which normally control both maturation of cells and their release from the marrow.¹³ Leya has advanced the idea that panmyelopathy (panmyelophthisis), either primary or secondary, will eventually lead to marked reactive myeloblastic proliferation with leukemia, if the patient survives long enough.³

Recently Block and his associates,⁷ Meacham and Weisberger⁹ and Mallarmé⁵ have independently expressed the opinion that the preliminary phase is irrevocably linked to the development of acute leukemia and that it constitutes a preleukemic phase. These authors all emphasize that the classical stigmata of leukemia are absent during the prelude. Both Block and associates⁷ and Mallarmé⁵ suggest that, prior to the introduction of modern supportive measures, the majority of these individuals died in the preleukemic phase and that the

disease was not allowed to complete its course. Therefore Mallarmé anticipates that cases of acute leukemia preceded by a period of hematologic abnormality will now be encountered with greater frequency.⁵

If a definite preleukemic phase of acute myeloblastic leukemia could be defined, it would have great significance and it is possible that anti-leukemic agents might be more efficacious during such a period. From a purely diagnostic standpoint, delineation of a panmyelopathic preleukemic phase of acute myeloblastic leukemia would be most desirable as these cases could then be separated from unexplained refractory anemias, neutropenias and thrombocytopenias. In this connection, it should be recalled that Valentine and his group have shown that leukocytes in acute and chronic myelogenous leukemia and in myeloproliferative disorders exhibit distinct and characteristic biochemical patterns.¹⁴⁻¹⁷ It is possible that if leukocytes of cases of this type could be studied biochemically during the preliminary phase, enlightening information might be obtained. Such studies might indicate whether or not a relationship exists between the leukocytes at this stage and those of fullblown leukemia.

In conclusion, this case has been reported to reemphasize that a prolonged period of blood disorder may precede the development of myeloblastic leukemia. Attention is directed to the need for investigation to determine whether or not blood disease, which is succeeded by leukemia, is irrevocably linked to the neoplastic process.

SUMMARY

A case with a prolonged period of blood disorder preceding the terminal development of myeloblastic leukemia is reported in some detail. The preleukemic period was characterized by anemia, neutropenia and thrombocytopenia. It extended over a period of almost nine years but was punctuated by a period of remission lasting four and one half years. In the initial phase, the marrow was hypoplastic but during the later stages, it was hyperplastic.

Brief reference is made to somewhat similar cases that have been recorded and to the ideas expressed by the authors of these reports.

It is suggested that further investigation is needed to determine whether the initial blood disease occurring in such cases is irrevocably linked to the subsequent leukemia.

SUMMARIO IN INTERLINGUA

Es reportate in detalio un caso in que un prolongate disordine hematologic precedeva le disveloppamento terminal de leucemia myeloblastic. Le periodo preleucemic esseva characterisate per anemia, neutropenia, e thrombocytopenia. Illo durava quasi nove annos sed esseva interrompate per un periodo de remission de quatro e medie annos. In le phase initial, le medulla esseva hypoplastic; durante le stadios plus avantiate, illo esseva hyperplastic.

Es discutite brevemente le reportos de casos comparabile in le litteratura. Le ideas exprimite per lor autores es notate.

Investigationes additional pare necesse pro determinar si le morbo initial del sanguine in tal casos es irrevocabilmente associate con un leucemia subsequente.

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