Acute Monoblastic Leukemia: Diagnosis and Treatment of Ten Cases

By Robert W. McKenna, Clara D. Bloomfield, Fred Dick, Mark E. Nesbit, and Richard D. Brunning

During a large clinicopathologic study of acute nonlymphocytic leukemia (ANLL), ten patients were identified in whom the leukemic blasts demonstrated striking morphologic and cytochemical similarities and who seemed to form a specific subgroup of ANLL. The patients' leukemic blasts were studied in routine blood and bone marrow preparations and by cytochemical and ultrastructural techniques. In routine smears, the blasts showed no clear evidence of differentiation. Cytochemically, the blasts exhibited strongly positive nonspecific esterase activity, which was completely inhibited by incubation with sodium fluoride, and were myeloperoxidase and sudan black B negative. Ultrastructural features of the blasts were similar to those described for monocytic leukemias. Striking clinical features included the occurrence primarily in young patients, the high frequency of lymphadenopathy at presentation, and the high incidence of post-treatment disseminated intravascular coagulation. Complete remissions were frequently initially obtained with daunorubicin in combination with various other agents and later in the disease with VP16-213. Based on the cytochemical and ultrastructural features, we concluded that this form of ANLL was a variety of acute monocytic leukemia. Recognition of the entity is important for optimal therapy.

There is increasing interest in distinguishing the different cytologic types of acute leukemia because of their varying clinical courses and responses to therapy. Certain subgroups of acute nonlymphocytic leukemia (ANLL), such as acute promyelocytic leukemia and erythroleukemia, have been distinguished as morphologic and clinical entities. This report describes ten patients with a form of ANLL in which the leukemic cell population consists of primitive-appearing blasts which exhibit striking morphologic, cyto-

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Submitted March 10, 1975; accepted April 30, 1975.

Supported in part by the Leukemia Research Fund, Inc. of the University of Minnesota, USPHS Grant No. CA-08832 from the National Cancer Institute, the Masonic Hospital Fund, Inc., and the American Cancer Society.

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Table 1. Clinical Manifestations

<table>
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<th>Patient No.</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Fever</th>
<th>Weakness</th>
<th>Bleeding*</th>
<th>Infection</th>
<th>Lymphadenopathy</th>
<th>Hepatomegaly</th>
<th>Splenomegaly</th>
<th>DIC</th>
<th>Treatment (mo)</th>
<th>Survival (mo)</th>
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*Present, +; not present, 0.
*Bruising or petechiae, a; bleeding, b; disseminated intravascular coagulation (DIC), c.

chemical, and ultrastructural similarity (Table 1). Based primarily on the nonspecific esterase reactivity of the blasts, this group of acute leukemias appears to represent a form of monocytic leukemia, and will be referred to in this report as acute monoblastic leukemia.

MATERIALS AND METHODS

Eight of the ten patients in this report were from a population of 193 cases of acute nonlymphocytic leukemia diagnosed and treated at the University of Minnesota Hospitals between December 1, 1964 and November 30, 1974. Forty-four of the 193 patients were less than 16 yr of age. The blood and bone marrow smears of the other two patients (7 and 8) were from the consultation files of one of the authors (R.D.B.). The patients were selected on the basis of the morphology of the leukemic blasts in Wright-stained smears of blood and bone marrow and by the cytochemical characteristics of these cells.

In addition to Wright-Giemsa stain, the following special cytochemical procedures were utilized: nonspecific esterase (NSE) using alpha-naphthyl acetate as substrate, pre- and postincubation with sodium fluoride;4 acid phosphatase (AcP) by the method of Li et al.;5 pre- and postincubation with tartaric acid6; peroxidase by Kaplow’s technique;7 sudan black B (SBB); chloroacetate esterase (CAE) using a modification of Leder’s method;8 periodic acid-Schiff (PAS); and methyl green pyronin (MGP) by Perry and Reynolds’s modification of Kurnick’s technique.9 All of the cytochemical studies were performed on initial pretreatment blood and bone marrow smears.

All of the above cytochemical procedures were performed on blood or bone marrow smears in six of the patients. Because of insufficient material or too great a time interval for valid cytochemical staining, some of the procedures were not performed in four of the patients.

Hematoxylin- and eosin-stained sections of bone marrow were studied in all patients; ultrastructural studies were performed in three. Specimens for electron microscopy were processed by a method previously described.10 The clinical course of all patients was reviewed.

RESULTS

Blood

The hematologic values at the time of diagnosis are listed in Table 2. Nine of the ten patients presented with anemia. The degree of anemia was slight to moderate in most instances. The median hemoglobin value for the group was 9.5 g/dl. The leukocyte counts range from 1.6 x 10⁹/liter to 365.0 x 10⁹/liter. Six patients were leukopenic, three had leukocytosis, and one had a normal leukocyte count. The median platelet count for the group was 114.0 x 10⁹/liter.
The blasts were morphologically uniform in each patient and were remarkably similar from one patient to the next. They were large, generally 18–25 μ in diameter, with abundant blue-gray cytoplasm. Many of the cells showed a dust-like azurophilic granulation in the cytoplasm and very fine vacuolization (Fig. 1). Occasional cells demonstrated cytoplasmic extensions. There was often considerable cytoplasmic shedding with numerous particles of bare cytoplasm scattered across the smear. This finding was particularly apparent when the peripheral blast count was high. The nucleus was round or slightly oval in shape with a reticular chromatin pattern, and either centrally or eccentrically located in the cell. One to four light-blue nucleoli could usually be identified in the nucleus. When the nucleolus was single, it was often very prominent and cen-

**Table 2. Pretreatment Laboratory Values**

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<th>Patient Number</th>
<th>Hgb (g/dl)</th>
<th>Platelets (x 10^12/liter)</th>
<th>WBC (x 10^9/liter)</th>
<th>Blasts (%) Blood Marrow</th>
<th>Muramidase (LYSOZYME) (μg/ml) Normal 2.0 - 11.9</th>
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ND, not done.

![Fig. 1. This blast is from the blood of patient 6. Note the prominent nucleolus and abundant cytoplasm containing fine azurophilic granulation. Wright-Giemsa. x 1000.](image-url)
trally located. There was no evidence of differentiation of blasts to monocytoid cells, monocytes, or neutrophils in routine smears. No Auer rods were identified in the blasts from any of the patients even after prolonged search.

**Bone Marrow**

The bone marrow was markedly hypercellular in all of the patients, and trephine biopsy sections exhibited complete replacement of the marrow. In the sections, the blasts were large with abundant eosinophilic cytoplasm, large round nuclei, and prominent eosinophilic nucleoli (Fig. 2). In the bone marrow smears, the percentage of blasts varied from 74% to 98%, with a median of 95%. Morphologically, they were identical to those in the peripheral blood (Fig. 3). In the bone marrow, as in the blood, Auer rods were not identified, and the leukemic blasts showed no apparent differentiating features. The mature neutrophils and neutrophil precursors, which were present, showed normal cytoplasmic granulation and nuclear lobulation. There was no increase in monocytes in any of the bone marrows, and no evidence of increased immature cells with monocytic features could be found. The lymphocytes were normal in appearance, and immature forms could not be found. Prior to performing special cytochemical procedures, the cases were thought to be unclassifiable or undifferentiated acute leukemias. Repeat bone marrow examinations at various times during the course of the disease of four patients failed to show any evidence of differentiation of the leukemic cells.

**Cytochemistry**

*Non specific esterase (NSE).* The cytochemical characteristics of the blasts are shown in Table 3. The blasts of all of the patients stained positive with the alpha-naphthyl acetate reaction. The distribution of the stain was diffuse, finely
Fig. 3. The blasts depicted here are from the bone marrow of patient 9. They are morphologically uniform with relatively abundant cytoplasm, oval nuclei, and an absence of nuclear folding. Wright-Giemsa. x 1000.

granular, and uniform throughout the cytoplasm of the cells (Fig. 4). Individual blasts varied in their affinity for the stain from slightly to intensely positive. The majority of the blasts in each of the most recent patients showed a strongly positive staining reaction. In the first two patients of the series (Nos. 1 and 2), unstained smears of bone marrow had been stored for 8 and 9 yr prior to staining for NSE, and there was a slight to moderate degree of reactivity. When the staining procedure was repeated following sodium fluoride incubation, the NSE activity was completely inhibited in the blasts in nine of the ten patients. In one of the ten patients, the intensity decreased from strongly positive to weakly positive.

Acid phosphate (AcP). Seven of eight patients whose smears were stained for

Table 3. Cytochemistry of Leukemic Blasts

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<th>Patient Number</th>
<th>NSE</th>
<th>NSE-F1</th>
<th>AcP</th>
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+++ strongly positive; ++, moderately positive; +, weakly positive; ±, equivocal; 0, negative; ND, not done; NSE, nonspecific esterase; NSE-F1, nonspecific esterase with fluoride inhibition; AcP, acid phosphatase; AcP-T, acid phosphatase with tartrate inhibition; SBB, sudan black B; CAE, chloroacetate esterase; PAS, Periodic Acid Schiff; MGP, methyl green pyronin.
A

B

Fig. 4. (A) The blasts in this bone marrow smear from patient 5 show strongly positive esterase activity. Many of the blasts stain more intensely than normal monocytes. Alpha-naphthyl acetate. × 1000. (B) When sodium fluoride is added to the staining mixture, the esterase activity is completely inhibited. Alpha-naphthyl acetate postfluoride incubation. × 1000.

AcP activity demonstrated a positive reaction in their blasts. The stain was characterized by small, sometimes irregularly shaped granules scattered diffusely throughout the cytoplasm and overlying the nucleus (Fig. 5). Nearly all of the blasts showed some degree of positivity which was completely abolished when tartaric acid was added to the staining mixture. The blasts from all except the earliest patient studied showed AcP activity. The smears from this patient had been stored for 8 yr prior to staining.
Fig. 5. (A) The acid phosphatase (AcP) stain of the blasts from patient 6 is strongly positive. Acid phosphatase, x 1000. (B) The AcP activity is completely inhibited by tartaric acid. Acid phosphatase posttartaric acid incubation. x 1000.

Peroxidase and Sudan black B (SBB). In all but three patients, the leukemic blasts were completely negative for peroxidase and SBB. Rare blasts of one patient showed equivocally positive peroxidase reactions. Occasional blasts of two other patients demonstrated equivocal SBB positivity.

Chloroacetate esterase (CAE). Most of the blasts in all of the patients manifested a diffuse uniform reactivity. The degree of reactivity was slight.

Periodic acid-Schiff (PAS). The PAS stain was performed in eight patients. Three showed moderately positive-staining blasts, three weakly positive, and
Fig. 6. Leukemic cells in a bone marrow specimen from patient 10. The cytoplasm is abundant and is irregularly distributed around the nucleus. The nucleus is generally round or oval with peripheral condensation of the chromatin. Uranyl acetate and lead citrate. x 4800.

two were negative. The distribution of the reaction was identical in all cells; small granules were scattered throughout the cytoplasm.

*Methyl green pyronin (MGP).* The blasts of all eight patients whose smears were stained with MGP were positive. The distribution of stain was diffuse and uniform throughout the cytoplasm in nearly all of the blasts.

**Ultrastructure**

The ultrastructural features of the leukemic cells were similar in the three patients studied. The cytoplasm was abundant and frequently showed an irregular distribution around the nucleus (Fig. 6). There were numerous free ribosomes, mitochondria, and strands of rough endoplasmic reticulum. Azurophil granules were found in varying numbers in many of the cells, and fibrillar arrays, frequently in a paranuclear location, were noted in a large number of the blasts (Figs. 7 and 8). Ribosome-lamella complexes were found in 90% of the blasts in one patient and in 30% of the blasts in another patient.\textsuperscript{11} The nuclei
Fig. 7. Blasts in a blood specimen from patient 9. The cytoplasm is somewhat less abundant and more regularly distributed around the nucleus than in the cells in Fig. 6. The nuclei are large, and the sparse chromatin is peripherally distributed. Fibrillar arrays (↑) are noted in several cells. Uranyl acetate and lead citrate. × 6000.

were frequently round or oval. Occasional nuclei showed one or more indentations; a small number of cells exhibited deep folding or clefting. In the majority of cells, the nuclear chromatin showed a peripheral condensation. One to four fairly prominent nucleoli were noted.

Clinical Features

The clinical features and survival for each patient are listed in Table 1. The sex distribution was equal. All of the patients were less than 31 yr of age at the time of diagnosis; five were less than 16. One patient (No. 6) was successfully treated with prednisone and testosterone for aplastic anemia secondary to chloramphenicol 11 yr prior to the development of leukemia.

Presenting symptoms included fever and weakness in all patients and docu-
Fig. 8. High magnification of a blast from patient 9. The abundant cytoplasm contains numerous free ribosomes, several mitochondria, and many azurophil granules. A fibrillar array can be noted in a paranuclear location. Uranyl acetate and lead citrate. × 13,000.

mented infections in most. Bleeding was a presenting complaint in seven patients. In three of these, the bleeding consisted only of petechiae and ecchymoses. Four patients had more extensive bleeding. One patient presented with disseminated intravascular coagulation (DIC); pretreatment screening studies for DIC were not performed on the remainder of the patients. Lymphadenopathy was present at diagnosis in nine of the patients. In eight, the lymphadenopathy was generalized and bulky; in one, it was localized and "shotty." Seven of the ten patients presented with hepatosplenomegaly.

Four patients developed laboratory-confirmed DIC following initiation of chemotherapy; two other patients (Nos. 1 and 2) showed clinical evidence of DIC, but the appropriate laboratory tests to confirm this were not performed. The serum muramidase (lysozyme) was elevated in four patients and normal in two.

Because of the long time period over which these patients were seen, the
treatment regimens varied. Five of the ten patients obtained initial complete remissions: one with daunorubicin and prednisone, one with vincristine and prednisone, two with daunorubicin and cytosine arabinoside plus prednisone, and one with daunorubicin, methotrexate, prednisone, and vincristine. The median duration of complete remission was 5 mo (range, 1-20 mo). VP16-213 was used for reinduction in two patients; both obtained complete remissions.

Five of the patients survived 1 mo or less. Three of them expired during induction chemotherapy with DIC. The remaining five patients have lived from 4+ to 38 mo; three are still living (Table 1).

**DISCUSSION**

The origin of monocytic leukemia has been a matter of considerable controversy in past years. Naegeli believed that all monocytic leukemias were varieties of myelogenous leukemia. Schilling proposed that all monocytic leukemias were derived from the reticuloendothelial system. As a result, Downey introduced the term Naegeli's monocytic leukemia to describe those monocytic leukemias which appeared to be myeloid in origin and Schilling's monocytic leukemia to describe those leukemias which appeared to have a reticuloendothelial origin. Current knowledge derived from cell kinetic studies, bone marrow cultures, cytochemistry, and ultrastructural studies have supported the myeloid origin of the monocyte. The heterogeneous morphologic expression that the monocytic leukemias may manifest does not contraindicate a common genesis in the myeloid system.

The distinctiveness of the type of acute leukemia described in this report is based on the uniformity of the morphologic and cytochemical features of the leukemic blasts. The clinical findings, though less consistent than the morphology and cytochemistry, still manifest a certain degree of unity with regard to age, symptoms, physical findings, laboratory values, and response to therapy.

**Morphology**

The morphology of the leukemic cells in this study differs from other descriptions of monocytic leukemias. Kass and Schnitzer describe the malignant monocyte as a cell with multiple nucleoli, multiple nuclear lobulations, histiocytic-type nuclear chromatin, cytoplasmic tailing, multiple pseudopodia devoid of granules, and aggregates of granules in a perinuclear distribution. Other descriptions are similar to this.

The leukemic blasts of all of the patients in this report failed to show clear evidence of differentiation along monocytic lines based on the usual morphologic features. The diagnosis of acute monoblastic leukemia was made only after special cytochemical studies identified the intense nonspecific esterase activity in the blasts.

The ultrastructure of monocytic leukemia has been described by Freeman and Journey and Kass and Schnitzer. The blasts in our group of leukemias demonstrate many of the ultrastructural features described for acute monocytic leukemias. The ribosome–lamella complexes are similar to those described by Katayama et al. in the hairy cells of leukemic reticuloendotheliosis.
Cytochemistry

Normal monocytes exhibit NSE activity in their cytoplasm when alpha-naphthyl acetate is used as the substrate. Granulocytes contain little or no esterase activity with this substrate. The NSE activity of monocytes can be completely inhibited by sodium fluoride incubation. The leukemic cells in myelomonocytic leukemia and “pure” monocytic leukemia have been shown to exhibit the same nonspecific esterase-staining characteristics as normal monocytes. The intensity of the NSE reaction of leukemic monocytes occasionally exceeds that observed in normal blood monocytes. The leukemic blasts in all of the patients in this series demonstrated NSE activity which was inhibited by sodium fluoride. The NSE reaction in the blasts in this group of patients was more intense than that seen in normal monocytes. This uniform, intense NSE activity in the leukemic cells, combined with their striking morphologic uniformity, was the basis for distinguishing this group of leukemias as a specific entity, acute monoblastic leukemia.

The remainder of the cytochemical reactions were consistent from patient to patient and provided added emphasis to the homogeneity of these leukemias. Most of the patients in this report whose blasts were studied for AcP activity exhibited a moderate to strong reaction which was inhibited by tartaric acid. These results were consistent with the findings of Yam et al. in acute monocytic leukemia.

Blasts of acute monocytic leukemias are usually reported as staining negative or weakly positive with peroxidase and sudan black B. Schmatzl et al. have proposed that the variable degree of peroxidase and sudan positivity in monocytic leukemias is related to the varying number of azurophilic granules present within the leukemic monocytes. All of our patients had azurophilic granulation in the cytoplasm of their blasts, and this granulation was not related to the presence of peroxidase and sudan positivity.

CAE activity is usually negative in normal monocytes, although at times a small amount of reactivity is present. Blasts in acute monocytic leukemia exhibit weak or negative reactivity with a naphthyl-AS-D chloroacetate substrate. The blasts from our patients showed weak CAE activity.

Using cytochemical techniques, Leder has demonstrated a considerably higher percentage of monocyte precursors in normal bone marrow than previously appreciated. The simultaneous demonstration of peroxidase, NSE, and CAE activity in the same bone marrow cell has been accomplished. The implication of this finding is that intermediate forms between a common precursor cell and more differentiated monocytes and granulocytes may exist and manifest the cytochemical reactions of both cell lines. It is likely that the leukemic blasts in the present group of patients are just beyond the intermediate cell described by Leder, at a stage of differentiation too early to be recognized in routine blood and bone marrow smears.

Clinical Features

The striking clinical features of this subclass of ANLL are the occurrence primarily in young people, the high frequency of lymphadenopathy at presentation, and the high incidence of post-treatment DIC. Among the types of ANLL,
only acute myelomonocytic leukemia has had a similar incidence of presenting lymphadenopathy. Aside from acute promyelocytic leukemia (APL), we have found no other subclass of ANLL associated with such a high incidence of post-treatment DIC.

The ultimate test of any pathologic classification or morphologic entity is its clinical utility. Based on the cytochemical identification of the blasts as monocytic in nature, VP16-213, an agent reported to be effective in monocytic leukemia, was used for reinduction in two recent patients who developed resistance to conventional agents (daunorubicin and cytosine arabinoside); both patients obtained a complete remission. To date, we have had no success with VP16-213 in other types of ANLL resistant to standard therapy.

The importance of identifying subtypes of leukemia which have a strong likelihood to develop DIC with treatment is well illustrated by the recent striking improvement in survival in APL. Through the judicious use of heparin, many patients with APL who previously expired with DIC now survive induction therapy. Three of our early patients with acute monoblastic leukemia expired during induction chemotherapy with DIC. Because of our current awareness of this problem in this type of leukemia, a recent patient has been successfully managed through two separate induction courses complicated by severe DIC. Early institution of low-dose continuous heparin therapy along with large amounts of cryoprecipitate and fresh-frozen plasma prevented significant bleeding. Thus, though acute monoblastic leukemia is an uncommon variant of ANLL, recognition of it as a separate entity would appear to be important from a therapeutic viewpoint.

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