Acute Myelofibrosis—A Leukemia of Pluripotent Stem Cell*

A Report of Three Cases and Review of the Literature

DAVID M. AMBERGER, M.D., ABDUS SALEEM, M.D., BONNIE L. KEMP, M.D., and LUAN D. TRUONG, M.D.

Department of Pathology, Baylor College of Medicine, Houston, TX 77030

ABSTRACT

The histogenesis of blasts in acute myelofibrosis is generally regarded to be of megakaryocytic origin. Three case reports are presented and 19 other reported cases are reviewed from the literature where the cells of origin appear to be myeloblasts, myelomonoblasts, lymphoblasts, or undifferentiated blasts. It is therefore postulated that acute myelofibrosis is a hemopoietic stem cell disorder, and acute megakaryocytic leukemia (FAB-M7) represents one subset of the disorder.

Introduction

Lewis and Szur, in 1963, described five patients who had a rapidly fatal clinical course. These patients had absence of adenopathy and massive hepatosplenomegaly, pancytopenia, peripheral myeloblastosis, minimal changes of red blood cell morphology, and bone marrow similar to that of chronic myelofibrosis. This rare entity termed "malignant myelosclerosis" was considered an acute and malignant variant of chronic myelofibrosis.10,11 Since that first report this clinical entity has undergone many name changes; the most frequently used is "acute myelofibrosis." In the more recent literature, many investigators have tried to prove that the histogenesis of the blasts present in the bone marrow and occasionally in the peripheral smear are of megakaryocytic origin. These investigations have employed such techniques as electron microscopy, immunoperoxidase and cytogenetic studies.1,2,3,4,5,6,8,9,13,14 Three cases are reported and a review of the literature with the postulation that acute myelofibrosis could be of a pluripotent stem cell origin.

Case Report (1)

A 65-year-old Caucasian man presented to his local physician with a three-week history of increasing shortness of breath, generalized weakness, and pallor. The family history and past medical history were unremarkable. The physical examination revealed no splenomegaly, adenopathy or hepatomegaly. The rest of the physical examination was unremarkable. The hemoglobin was 4.8 g per dl, hematocrit 14.3 percent, white blood cell 2.1 × 10^9 per L with 64 percent segmented neutrophils, 13 percent bands,
35 percent lymphocytes; platelet count 22 × 10⁹ per L. The peripheral smear showed a few teardrop cells, moderate anisopoikilocytosis and no nucleated red blood cells. The bone marrow aspirates were described as "dry taps." Bone marrow biopsy showed almost 100 percent cellularity. About 70 percent of cells in the bone marrow were blasts. Touch prep showed some blasts to be positive for chloracetate esterase. Immunoperoxidase stain for VIII antigen was negative in blasts. Only rare erythroid and mature myeloid forms were present. Reticulin stain showed a diffuse, moderate increase in reticulin. Rare megakaryocytes were seen which exhibited no atypia. The diagnosis of acute myeloblastic crisis with acute myeloid leukemia was made. The patient was treated with ARA-C, Allopurinol, Acyclovir, Ticarcillin, Tobramycin, and Dimetap. He required multiple transfusions with packed red blood cells and platelets. His WBC count declined to 0.5 × 10⁹ per L with 100 percent lymphocytes. His hospital course was complicated with mild temperature elevations. A repeat bone marrow biopsy two weeks after initial chemotherapy revealed hypocellular marrow with 10 to 15 percent myeloblasts and slightly increased numbers of mature granulocytic forms.

Three weeks after the patient’s initial chemotherapy, he was readmitted for re-induction chemotherapy. On admission he was found to be severely neutropenic (WBC 0.2 × 10⁹ per L) with a temperature of 101.4°F. Blood culture showed Klebsiella bacteria and urine cultures were positive for Escherichia coli. Despite aggressive treatment, he continued to be septic. He experienced a rapid decline with development of bronchopneumonia, gastrointestinal bleeding refractory to platelet transfusions, acute respiratory distress syndrome, and frequent cardiac arrhythmias. The patient died of cardiopulmonary arrest two months after his initial diagnosis.

Case Report (2)

A 50-year-old black male presented to his physician with complaints of progressive fatigue, fever to 102°, night sweats and a 15 lb weight loss over a period of four weeks. Physical examination showed a mild splenomegaly but no lymphadenopathy or hepatomegaly. Laboratory tests showed hemoglobin 7.5 g per dl, hematocrit 22.2 percent, platelet count 89 × 10⁹ per L, white blood cell 4.1 × 10⁹ per L with 37 percent segmented forms, 50 percent lymphocytes, eight percent bands, two percent monocytes, 3 percent myelomonocytes, 28 percent nucleated red blood cells per 100 white blood cells, and reticulocytes 0.8 percent.

The peripheral smear showed marked red cell anisocytosis with acanthocytes, tear drop cells, schistocytes, ovalocytes, numerous nucleated red blood cells, thrombocytopenia, and leukopenia. The bone marrow aspirate was a dry tap. The bone marrow biopsy was almost 100 percent cellular and showed diffuse marrow fibrosis, infiltration of immature myelomonocytic cells and rare atypical megakaryocytes. About 50 percent of blasts were muramidase positive. Blasts were negative for VIII antigen. Normal hematopoietic cells were markedly decreased and there was a background of a modest number of lymphocytes and plasma cells. A diagnosis of acute myelofibrosis with acute myelomonocytic leukemia was made.

The patient was begun on transfusion therapy and remained transfusion dependent receiving treatment every five weeks for the next 16 months. The patient at this time was hospitalized for fever, progressive anemia, thrombocytopenia, and increasing left upper quadrant pain. He was found to have a markedly enlarged spleen and moderate hepatomegaly. After a thorough work-up, his symptoms were attributed to splenic sequestration and probable splenic infarct. Splenectomy was performed. The spleen weighed 1500 grams and showed multiple small infarcts and prominent extramedullary hematopoesis. The patient was stabilized post surgery and was discharged. Three months later the patient developed a peripheral blast crisis with myelomonocytic blood picture confirmed by positive staining with chloracetate esterase and alpha-naphthyl butyrate esterase. He was placed on a chemotherapy regime with ARA-C. The patient responded to chemotherapy but soon developed a pancytopenia, a markedly decreased platelet count, and subsequently died with generalized sepsis and gastrointestinal bleeding.

Case Report (3)

A 62-year-old Latin American woman saw her physician with complaints of dizziness, weakness, and shortness of breath which had developed and progressed over a several months period. Work-up showed the patient to have diabetes mellitus, hypothyroidism, severe peripheral vascular disease, and a new onset anemia with hemoglobin of 9.0 g per dl and macrocytic indices. (Hemoglobin eight months earlier had been normal.) She was admitted to the hospital for further evaluation. On admission she had no splenic or hepatic enlargement. Laboratory examination showed hemoglobin 7.7 g per dl; hematocrit 22.9 percent, mean corpuscular volume 106.9; mean corpuscular hemoglobin concentration 35.9; white blood cell 5.0 × 10⁹ per L with 48 percent lymphocytes, 42 percent segmented forms, five percent bands, four percent monocytes and one percent eosinophils; platelets 120 × 10⁹ per L. The peripheral blood smear showed moderate anisocytosis, polychromasia, and macrocytes. A few stomatocytes and occasional stippled and nucleated cells were present. Platelets were adequate. No blasts were identified. The bone marrow biopsy showed many areas of necrosis involving both bony spicules and marrow elements. The cellularity of the viable hematopoietic cells ranged from 20 to 30 percent, most of which were immature myelomonocytic cells. There was maturation arrest with no significant number of mature granulocytes. Only a few erythroid precursors or megakaryocytes were seen. Diffuse fibrosis was present throughout the marrow spaces, confirmed by a reticulin stain. Immunopa-
oxidase stain for muramidase was positive in about 30 percent of cells and was negative for VIII antigen. A diagnosis of acute myelomonocytic leukemia with acute myelofibrosis was made.

The patient was transfused with three units of leukocyte poor packed red blood cells. She tolerated the transfusion well and a follow-up complete blood count showed a hemoglobin 13.1 g per dl with mean corpuscular volume of 100. She reported feeling stronger with no shortness of breath post transfusion. She was discharged to home on appropriate medications for her diabetes and hypothyroidism. She is currently transfusion dependent two months after her initial diagnosis.

**Review of the Literature**

In the majority of cases of acute myelofibrosis, the cell of origin is reported to be megakaryoblasts. However, there are a few reports in the literature where the blasts seen in the peripheral blood and/or bone marrow do not appear to be megakaryoblasts. Wood and Andrew in 1949 reported one case with acute myelofibrosis and myelosclerosis showing 24 percent blasts in peripheral blood and 31 percent blasts in bone marrow, morphologically identified as myeloblasts. The red blood cell morphology was not reported, but the peripheral blood showed seven percent nucleated red cells.

Castleman and McNeely reported a patient who gave a history of weakness, occasional night sweats, and anorexia with a weight loss of 28 lbs of five months duration. The blood picture showed anemia and thrombocytopenia. Bone marrow aspirate could not be obtained. The patient received antibiotics and supportive therapy but died 19 days after admission. At autopsy, the bone marrow showed large numbers of “reticulum” cells and only a few megakaryocytes. The matrix of the marrow was composed of delicate fibrillary reticulum. The lymph node, liver and spleen showed infiltration with reticulum cells. No extramedullary hematopoiesis (EMH) was seen.

Khan and Martin in 1968 reported one case of acute myelofibrosis with peripheral blood showing 95 percent myeloblasts. The marrow was a dry tap. Autopsy marrow showed extensive fibrosis and infiltration with myeloblasts.

Zittoun in 1972 reported nine cases of acute myelofibrosis showing extensive marrow fibrosis, decreased megakaryocytes and infiltration of blasts. Myeloblasts were identified in four cases, lymphoblasts in two cases, myelomonocytic precursors in one case, and undifferentiated blasts in two cases. The patients were given steroids, chemotherapy, and supportive treatment. Seven of his patients died between two weeks and eight months after presentation. Two patients, who had remission, were living 12 and 18 months after chemotherapy.

Polli in 1975 reported one case of acute myelofibrosis with myeloblastic infiltration of bone marrow. Lubin in 1976 reported three cases of acute myelofibrosis with marrow infiltration with myeloblasts. The bone marrow was a dry tap in all the three cases, and autopsy marrow showed extensive fibrosis, infiltration with myeloblasts, and decreased megakaryocytes. Extramedullary hematopoiesis was noted in the spleen and liver in all the three cases. The patients were treated with steroids and supportive therapy but died six weeks to 11 months after presentation. Bird and Proctor in 1977 reported one case of acute myelofibrosis. The bone marrow was fibrotic and infiltrated with myeloblasts. Megakaryocytes were decreased. The patient was treated with steroids but died 10 days after presentation.

Bartoli in 1979 reported one case of acute myelofibrosis. The peripheral blood and bone marrow showed myeloblasts which were positive for chloracetate esterase. The aspirate could not be obtained, but the biopsy showed extensive fibrosis. Cytogenetic studies showed trisomy of chromosome 8. The patient was treated with steroids but died six
weeks after presentation. Now we report three cases of acute myelofibrosis, one with acute myelocytic leukemia and two with myelomonocytic leukemia.

Summarizing the literature and including our cases (table I), there are 22 case reports of acute non-megakaryocytic leukemia with acute myelofibrosis. The hematologic data is incomplete or unsatisfactory in some of the reports and follow-up is not included. Thus, a firm diagnosis could be questioned. There has been no attempt to delete these cases but it should be pointed out that a mild reversible fibrosis has been noted in the bone marrow of patients with acute leukemia.

All 22 cases reveal: (1) pancytopenia, (2) bone marrow disease characterized by fibrosis sufficient to preclude aspiration, and proliferation of immature cells of hematopoietic cell lines, (3) rapidly fatal clinical course, (4) minimal red blood cell abnormalities on peripheral blood film, (5) absence or mild splenomegaly at presentation, and (6) decreased numbers of megakaryocytes with only a few mildly atypical megakaryocytes. The age range was from 22 to 84 with a mean age of 48.5 years. There were 15 males, seven females and one whose sex was not mentioned. Myeloblasts were reported in 14 cases. Three had undifferentiated blasts, two had lymphoblasts and three had myelomonocytic blasts present in the bone marrow.

### TABLE I

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age/ Sex</th>
<th>Hgb (g/dl)</th>
<th>MCH (x 10^{12}/L)</th>
<th>MCHC (g/dl)</th>
<th>Platelets (x 10^{9}/L)</th>
<th>Percent Peripheral Blasts</th>
<th>Type of Blasts in Bone Marrow</th>
<th>Marrow Fibrosis</th>
<th>H</th>
<th>S</th>
<th>LNE</th>
<th>Diagnostic Tests</th>
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H = Hematocrit  
M = MCHC  
S = Splenomegaly  
EM = Electron microscopy  
LNE = Lymphadenopathy  
LMB = Bone marrow  
NA = Not available  
CC = Cytogenetics  
HCT = Hematocrit  

Discussion

Acute myelofibrosis is a fulminating myeloproliferative disorder characterized by an acute onset of pancytopenia, medullary overgrowth of reticulin fibers and marrow infiltration by immature hemopoietic cells. With the advent of immunohistochemical and cytogenetic methods, the results of several studies concluded that the nature of the blast was of megakaryocytic origin. Recently acute myelofibrosis has been included in the FAB (French, American, and British) classification (M7) identifying the disease process as an acute megakaryocytic leukemia. Despite the evidence presented by several authors, some reports suggest that acute myelofibrosis is also associated with blast proliferation of hemopoietic cells other than megakaryoblasts. In a recent article, Hruban et al found several cases of acute myelofibrosis in which blasts were heterogeneous with regard to the expression of the phenotype. These blasts expressed megakaryocytic, myeloid, or erythroid phenotypes. Review of the literature (table I) indicates that of the 22 patients with acute myelofibrosis where the blasts other than megakaryoblasts were identified, myeloblasts were reported in 14, myelomonocytic cells in three, lymphoblasts in two, and undifferentiated blasts in three cases. Like acute megakaryocytic leukemia, all of these cases exhibit an acute clinical course, intense myelofibrosis, minimal organomegaly, and a rapidly fatal outcome. However, the infiltration of marrow showed hemopoietic stem cells other than megakaryoblasts. In fact, megakaryocytes were only rarely seen. It therefore appears that acute myelofibrosis is a disorder of pluripotent stem cell, which is capable of variable phenotypic expression, and perhaps acute megakaryocytic leukemia (FAB-M7) represents one subset of the disorder.

References


