Acute Leukemia in Idiopathic Sideroblastic Anemia: Response to Combination Chemotherapy

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Three patients with idiopathic sideroblastic anemia of variable duration developed acute leukemia. In two the leukemia was morphologically and histochemically myeloblastic, in one lymphoblastic. With combination chemotherapy remission was achieved in all three. The remission inductions were complicated by long periods of bone marrow suppression and the duration of remissions was brief (3, 2 and 3 months). Survival after diagnosis was 13, 10 and 9 mo, respectively. The ring sideroblast abnormality persisted during the leukemic and remission phases and transfusion requirements remained unaltered in the two patients with transfusion dependent anemia throughout their courses.

Idiopathic sideroblastic anemia (ISA) is generally refractory to hematinic substances and hematopoietic stimulants, frequently transfusion dependent, and usually stable for many years. However, approximately 10 per cent of individuals with this disorder have eventually developed acute leukemia. In most of the 14 well described patients who developed leukemia survival was less than 4 mo. Chemotherapy attempts have rarely been documented and currently used combination chemotherapy was employed only in one recently reported case.

We report the clinical course of three patients with ISA with subsequent leukemic evolution and their response to anti-leukemic combination chemotherapy.

MATERIALS AND METHODS

Hematologic examinations were performed according to standard methods. Ring sideroblasts in marrow aspirates were identified by Prussian blue stain. Histochemical staining of peripheral blood and marrow (periodic acid–Schiff, Sudan Black B, peroxidase, α-naphthyl acetate esterase, and chloroacetate esterase) was carried out as previously described. Bone marrow chromosome analyses were performed according to the method of Tjio and Wang. The chemotherapy regimens employed were those prescribed by the SWOG (Southwestern Oncology Group) acute leukemia protocols in use at the time at which these patients' treatment was initiated.

Case 1

A 61-yr-old white man had been followed and treated by the orthopedic service since 1956 for chronic osteomyelitis of the left humerus. In 1961, anemia was documented (Hb 10.8 g/dl). In 1970, two transurethral prostate resections were performed and in association with these six transfusions were given. The prostatic tissue revealed hyperplasia with foci of well differentiated adenocarcinoma. Subsequent hemoglobin concentrations ranged from 8.1 g/dl to 10.9 g/dl and the MCV from 111 fl to 116 fl; leukocyte counts were normal.

In March 1971, the persistent anemia was first evaluated by the hematology service. Physical examination revealed mild pallor; the liver span was 15 cm and the spleen tip was just palpable. The hemogram was as follows: Hb 10.9 g/dl, Hct 33.2%, MCV 112 fl, reticulocytes 1.4%, WBC 6,500/mm3 with a normal differential, and platelets 281,000/mm3. Red cell morphology consisted of marked anisopoikilocytosis, target cells, macrocytes, and a hypochromic cell population. A bone marrow aspirate showed erythroid hyperplasia (46% erythroid cells) with mild megaloblastic changes, markedly increased reticuloendothelial cell iron and 69% of erythroid cells were ring sideroblasts. The serum iron was 63 μg/dl, TIBC 198 μg/dl and transferrin saturation 32%. Serum folate was 2 ng/ml, serum vitamin B12 439 pg/ml, Co2+ vitamin B6, and pyridoxine 27%.

Serum protein electrophoresis and thyroid function tests were normal as were blood chemistries. There was no history of alcohol abuse.

Pyridoxine (100 mg/day) and folinic acid (1 mg/day) administration for 6 mo were without effect on the anemia. During the ensuing 2½ yr, five transfusions were given, and persistent intermittent flares of the osteomyelitis required chronic antibiotic administration. In August 1973, chemical diabetes was documented and liver biopsy revealed parenchymal iron overload typical of hemochromatosis without evidence of cirrhosis. The hemogram and a bone marrow aspirate were unchanged. A bone marrow chromosome analysis showed a majority of 25 cells examined to be diploid and two karyotypes had a possible Bq+ abnormality.

Beginning in April, 1974, 2–3 transfusions per month were required for symptoms of progressive anemia. In August 1974, the leukocyte count was 4,500/mm3, the differential revealed two blast cells and two myelocytes; the platelet count was 161,000/mm3. A marrow aspirate now showed 14.5% blast cells, 9.5% promyelocytes, and persistence of ring sideroblasts. During the subsequent 6 mo the percentage of peripheral blood and marrow blast cells progressively increased. In January 1975, the leukocyte count was 20,000/mm3, with 70% blasts, the platelet count had decreased to 93,000/mm3 and the marrow was infiltrated with 90% blast cells with histochemical characteristics of myeloblasts (Table 1). Repeat chromosome analyses in September 1974 and January 1975 remained unchanged from the initial study. At this time chemotherapy was instituted with vincristine, 2 mg (iv), prednisone, 60 mg (po) per day for 2 wk and cytosine arabinoside, 200 mg/m2 (iv, continuous infusion) per day for 5 days (Fig. 1). The subsequent course was followed by disappearance of excess blast cells and severe bone marrow hypoplasia. Intermittent epistaxes were controlled with platelet transfusions and a left lower lobe pneumonia responded to antibiotics. By April 1975, the platelet count was 225,000 but moderate leukopenia and marrow hypoplasia of the myeloid series persisted. Cytosine arabinoside was...
ankles. He denied the use of alcoholic beverages. Physical examination consisted of malaise, a 5 lb. weight loss and occasional swelling of the ankles. A complete blood count revealed anemia which had first been noted in March 1974, and which was unresponsive to iron and vitamin B12 therapy. His symptoms consisted of mild pallor, mild tanning of the sun exposed skin and scattered 0.5–1.0 cm, soft cervical and axillary lymph nodes. The hemogram was as follows: Hb 9.9 g/dl, Hct 30.2%, MCV 103 fl, reticulocytes 1.6%, WBC 4,000/mm³ with a normal differential, and platelets 335,000/mm³. The erythrocytes showed mild anisopoikilocytosis as well as macrocytes, micromegocytes and hypochromia. The bone marrow aspirate was normocellular with increased numbers of megakaryocytes and mild erythroid hyperplasia; the iron stain revealed normal iron stores and 62% of erythroid cells were ring sideroblasts. A direct bone marrow chromosome analysis of 25 spreads and two karyotypes were normal. The serum iron was 132 μg%, TIBC 219 μg%, transferrin saturation 60%. The serum vitamin B₁₂ was 560 pg/ml. The chest x-ray showed apical thickening and an abdominal film splenomegaly and evidence of chronic hepatocellular disease. Radiographs of the upper and lower intestinal tract, the gall bladder and an intravenous pyelogram were normal. The electrocardiogram and vectorcardiogram were suggestive of an old posterior myocardial infarction. A cervical lymph node biopsy revealed reactive hyperplasia.

Over the ensuing 4 mo administration of pyridoxine (100 mg/day) and folic acid (1 mg/day) had no effect on the anemia. In November 1974, when the hemoglobin was 8.1 g/dl and hematocrit 26.7%, a 2-wk trial of pyridoxal phosphate (30 mg every 6 hr subcutaneously) also produced no erythropoietic effect. Beginning in December 1974, when the hemoglobin had decreased to 7.7 g/dl, regular transfusions were necessary for symptoms of anemia, and he received approximately 2 units of red cells per month for the subsequent 1½ yr. During this period the leukocyte count and differential remained normal but the platelet count increased and varied from 650,000 to 950,000/mm³. A trial of nandrolone decanoate for 4 mo failed to reduce the transfusion requirements.

In July 1976, on a routine followup visit, the leukocyte count had risen to 31,800/mm³, consisting of 60% blast cells. A bone marrow aspirate also contained 67.5% blast cells and histochemical stains of these were characteristic of lymphoblasts (Table 1). Four days later the WBC count had increased to 100,000/mm³ and chemotherapy was initiated with adriamycin 40 mg/m² (iv), vincristine, 2 mg (iv) weekly, cytosine arabinoside, 70 mg/m² (iv, continuous infusion) per day for 7 days and prednisone, 200 mg (po) per day for 14 days followed by 60 mg per day for 14 days (Fig. 2). Three weeks later the marrow remained cellular, containing many blasts, and another

Case 2

A 67-yr-old white man was referred in July 1974, for evaluation of anemia which had first been noted in March 1973, and which was unresponsive to iron and vitamin B₁₂ therapy. His symptoms consisted of malaise, a 5 lb. weight loss and occasional swelling of the ankles. He denied the use of alcoholic beverages. Physical examination was remarkable only for mild pallor, mild tanning of the sun exposed skin and scattered 0.5–1.0 cm, soft cervical and axillary lymph nodes. The hemogram was as follows: Hb 9.9 g/dl, Hct 30.2%, MCV 103 fl, reticulocytes 1.6%, WBC 4,000/mm³ with a normal differential, and platelets 335,000/mm³. The erythrocytes showed mild anisopoikilocytosis as well as macrocytes, micromegocytes and hypochromia. The bone marrow aspirate was normocellular with increased numbers of megakaryocytes and mild erythroid hyperplasia; the iron stain revealed normal iron stores and 62% of erythroid cells were ring sideroblasts. A direct bone marrow chromosome analysis of 25 spreads and two karyotypes were normal. The serum iron was 132 μg%, TIBC 219 μg%, transferrin saturation 60%. The serum vitamin B₁₂ was 560 pg/ml. The chest x-ray showed apical thickening and an abdominal film splenomegaly and evidence of chronic hepatocellular disease. Radiographs of the upper and lower intestinal tract, the gall bladder and an intravenous pyelogram were normal. The electrocardiogram and vectorcardiogram were suggestive of an old posterior myocardial infarction. A cervical lymph node biopsy revealed reactive hyperplasia.

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| PAS | negative | positive | negative |
| Peroxidase | positive | negative | positive |
| Sudan black B | positive | ND* | ND |
| Naphthol AS-D | negative | negative | negative |
| α-Naphthylacetate | negative | negative | ND |

*ND, not determined.
course of adriamycin and cytosine arabinoside at the same dosages was given. The induction therapy was complicated by a sialadenitis, which responded well to broad spectrum antibiotics, and also by an inferoseptal myocardial infarction. Approximately 28 units of red cells and 20 platelet transfusions were required during this period. Followup marrow aspirates remained markedly hypocellular until October 1976, when the bone marrow cellularity and differential were normal; however, the ring sideroblasts remained. At this time, the leukocyte count was 2,600/mm³ (60% PMN’s, 19% lymphocytes, 19% monocytes and 2% eosinophils) and the platelet count was 330,000/mm³. Maintenance chemotherapy was begun with 6-mercaptopurine, 100 mg per day, and methotrexate, 15 mg per week, as well as intrathecal methotrexate. Regular red cell transfusions were required and leukemic remission persisted for 3 mo. In January 1977, the leukocyte count was 4,400/mm³, the platelet count was 620,000/mm³ but 10% blast cells were noted in the peripheral blood. The marrow was once again hypercellular and contained 24.5% blasts. In March 1977, remission induction was attempted with vincristine and prednisone. Six weeks later there was no response in that 31% blasts and 51.5% blasts persisted in the peripheral blood and bone marrow, respectively. Shortly thereafter, the patient was admitted to another hospital with chest pain and died in heart failure.

Chromosome analyses during the leukemic phase revealed marked aneuploidy, 56% and 16% of 25 spreads having 47 and 48 chromosomes, respectively. The extra chromosomes were in groups C and D.

Case 3

A 66-yr-old white man with a past history of rheumatoid arthritis presented with fatigue in February 1975. Physical examination was remarkable for mild pallor and a palpable spleen tip. The hemoglobin was 10.5 g/dl, the leukocyte count, 3,900/mm³ and platelet count, 178,000/mm³. The erythrocytes showed mild aniso- and poikilocytosis, macrocytes, and a few hypochromic microcytes. Bone marrow aspirate revealed erythroid hyperplasia, 75% of erythroblasts being ring sideroblasts. The hemogram remained unchanged for the ensuing 14 mo and no medications were prescribed.

In April 1976, the hemoglobin was still 10.2 g/dl; however, the leukocyte count had increased to 30,000/mm³, the differential revealed 80% myeloblasts by histochemical stains (Table 1) and the platelet count had decreased to 85,000/mm³. A bone marrow aspirate was hypercellular and contained 85% myeloblasts. Because of progressive anemia (Hb 5.8 g/dl) chemotherapy was initiated in August 1976, with vincristine, 2 mg (iv), adriamycin, 40 mg/m² (iv), prednisone, 100 mg (po) per day for 5 days and cytosine arabinoside, 70 mg/m² (iv) per day for 7 days (Fig. 3). After a transient thrombocytopenia, the platelet count returned to normal but leukopenia (WBC 1,600/mm³) persisted 6 wk later. At this time the marrow aspirate was hypocellular, containing only 1% myeloblasts and 34% erythroid precursors. Another course of adriamycin and cytosine arabinoside at reduced dosages (Fig. 3), as well as vincristine and prednisone, was followed 1 mo later by return of the peripheral leukocyte count and differential to normal. The marrow was normocellular with a normal differential except for mild erythroid hyperplasia and the persistence of ring sideroblasts. In November 1976, and in January 1977, two further courses of consolidation chemotherapy were given. Two weeks following the second of these, the patient developed acute pyelonephritis and died despite antibiotic therapy. Autopsy revealed disseminated candidiasis but no evidence of leukemia.

**DISCUSSION**

The development of acute leukemia in the course of ISA has been observed in occasional patients since the first description of the disorder by Björkman. A recent analysis indicates that the incidence of such leukemic transformation is relatively low, occurring in approximately 10 percent of cases; in two small series one fourth of patients developed acute leukemia. In contrast, patients who develop the ring sideroblast defect in the course of or after treatment of a neoplastic disease, such as multiple myeloma and Hodgkin’s disease, appear to almost uniformly acquire acute leukemia.

The time interval from onset of diagnosis of ISA to the appearance of leukemia has been highly variable, ranging from a few mo to 10 yr. Definite risk factors for this event have not been established. More severe anemia, a lower reticulocyte count, greater transfusion requirements and thrombocytopenia were more common in patients who died of leukemia in the largest analysis. In another series only a low serum iron concentration correlated with leukemic evolution. The appearance of hemoglobin H suggested a preleukemic phase of the disorder in two cases. Features of myeloproliferative or hypoplastic syndromes, disorders in which acute leukemia often evolves, have been prominent in some. Although thrombocytosis was thought to be a good prognostic sign in one analysis it has occurred in others who developed leukemia. Finally, various cytogenetic abnormalities have been found in approximately one half of patients with ISA but the majority of bone marrow chromosome analyses have been performed with nonbanded karyotyping. A nonrandom change has not been discovered and a chromosomal abnormality preceding leukemic
transformation has only been documented in three previous cases.\(^1,2\) In the three patients reported here documented ISA preceded the development of leukemia by \(1/2\) to \(3/2\) yr, two had transfusion dependent anemia and one had thrombocytosis.

The cytochemical features of blast cells in the leukemic phase of ISA have not been described with the exception of the recent report by Barton et al.\(^4\) whose patient had the typical characteristics of lymphoblastic leukemia. In the majority of patients the leukemic cell type was stated to be myeloid or the overall morphology resembled erythroleukemia.\(^3\) In our patients two had the typical histochemical features of myeloblastic leukemia and one of lymphoblastic leukemia. All three responded to the combination chemotherapy regimen in that the bone marrow morphology and peripheral blood normalized except for persistence of some leukopenia and the sideroblastic anemia. However, in all three patients recovery of marrow cellularity and the peripheral blood counts and achievement of leukemic remission was slow, ranging from 2–4 mo. Leukemic remission was short in two cases, relapse occurring at 2 and 3 mo, respectively, and was not evaluable in Case 3 as he died during remission. The lack of response to retreatment of the two cases with similar drugs suggests the appearance of early resistance of the leukemic clones.

ISA, like chronic granulocytic leukemia, appears to be a clonal disorder,\(^1\) and in both conditions, lymphoblastic as well as myeloblastic leukemia evolves. The persistence of ring sideroblasts and anemia after leukemic remission, as observed here and by Barton et al.\(^4\) resembles the persistence of the Philadelphia chromosome in chronic granulocytic leukemia when remission of the blastic phase is obtained. In contrast, the ring sideroblasts which accompanied acute granulocytic leukemia in a patient on presentation disappeared with remission of the leukemia.\(^2\) It is uncertain how prominent the ring sideroblasts were in this case and they may have represented only a minor abnormality. Although Maldonado reported iron laden mitochondria of erythroid precursors in preleukemic states and in frank leukemia,\(^3\) the majority of patients with ISA have a large percentage of marrow ring sideroblasts, almost always \(>40\%),\(^3\) and an accompanying hypochromic red cell population in the peripheral blood is a constant finding. Hast emphasized that intermediate sideroblasts (ferritin sideroblasts) are more often associated with impaired myeloid marrow colony forming capacity and leukemic evolution than the presence of typical ring sideroblasts in large numbers.\(^1\)

The limited experience to date with combination chemotherapy of the acute leukemia following an antecedent course of ISA indicates that the leukemic clone is susceptible to the currently used drugs. The short lived remissions as well as the prolonged periods of cytopenia in the ISA patients may be attributable to their advanced age and/or the underlying marrow disorder. The residual hemopoietic clone bearing the sideroblast defect appears to represent a cell line whose capacity to proliferate is impaired so that early leukemic relapse occurs.

REFERENCES

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