Chronic Myelogenous Leukemia Presenting in the Blastic Phase and Its Association With a 45 XO Ph^1 Karyotype

By Renuka Nigam and Harvey Dosik

A 58-yr-old male patient presented in the blastic phase of chronic myelogenous leukemia (CML). Cytogenetic studies revealed a 45 XO Ph^1 chromosome pattern in bone marrow cells during a short remission and again in the blastic phase of the disease. The patient expired 8 mo following diagnosis. The blastic phase of CML can simulate acute myelogenous leukemia (AML) clinically and hematologically; CML can be differentiated by the presence of the Ph^1 chromosome and the stigmata of CML. Absence of the Y chromosome from the bone marrow in CML is a recently described finding. Previous reports indicating the prevention of the blastic phase in patients with this karyotype could not be confirmed by our or other recently reported cases.

THE PHILADELPHIA CHROMOSOME represents a marker in most cases of CML.[1-3] Cases of CML without the Ph^1 chromosome are characterized by a more severe course and reduced median survival.[4] A third subgroup, i.e., CML associated with a 45 XO Ph^1 karyotype has recently been reported.[5] The present report concerns a case of CML presenting in the blastic phase and its association with a 45 XO Ph^1 karyotype.

CASE REPORT

N.P., a 58-yr-old white male, married with one child, presented in March 1973 with a 2-mo history of weight loss and fatigue. Physical examination revealed a well-developed, well-nourished male with petechiae on both lower extremities. The liver was palpable 5 cm below the right costal margin and the spleen 7 cm below the left costal margin. The hemoglobin was 10.4 g/100 ml, WBC 48,000/cu mm, platelets 33,000/cu mm, reticulocytes 7.5%. The differential count revealed 20% myeloblasts, 6% promyelocytes, 15% myelocytes, 16% bands, 11% neutrophils, 8% eosinophils, 17% basophils, 7% lymphocytes, and 28 nucleated red blood cells/100 WBCs. Bone marrow aspiration showed 86% myeloblasts. A diagnosis of acute leukemia, possibly the blastic phase of CML was made, and therapy with prednisone, 40 mg a day orally, was started.

In May 1973 he was seen at the Jewish Hospital and Medical Center of Brooklyn for the first time. At that time, he was asymptomatic. Physical examination revealed a spleen palpable 4 cm below the left costal margin. The hemoglobin was 13.7 g/100 ml, hematocrit 40%, WBC 36,700/cu mm, platelets 360,000/cu mm. Differential count was 9% myelocytes, 13% metamyelocytes, 13% bands, 45% neutrophils, 8% eosinophils, 7% basophils, 3% lymphocytes, and 2% monocytes. Bone marrow aspiration showed 2% blasts, 0.5% promyelocytes, 19% myelocytes, 27% metamyelocytes, 19% bands, 13.5% neutrophils, 6.5% eosinophils, 0.5% lymphocytes, and 12% normoblasts. Leukocyte alkaline phosphatase activity was 17 (control 40–120). LDH was 1650 units and serum B_{12} level was 3012 pg.

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Table 1

Date	Specimen	Cells Studied	Cells With 45 XO Ph^1 Karyotype	Cells With 46 XY Ph^1 Karyotype	Cells With 46 XY Karyotype	Clinical State
5/10/73	Bone marrow	18	15	1	1	Remission
6/4/73	Skin fibroblasts	20	None	None	20	Remission
6/11/73	PHA-stimulated peripheral blood	20	None	None	19	Remission
7/30/73	Bone marrow	13	12	1	None	Blastic phase

The patient remained symptom-free for 4 mo and steroids were gradually tapered. In July 1973, he was found to have generalized lymphadenopathy and an enlarging spleen. Although the hemoglobin and platelet counts remained normal, the WBC rose to 80,000/cu mm with 31% myeloblasts. In August 1973, he developed thrombocytopenia and treatment was begun with hydroxyurea, 6-mercaptopurine, and prednisone, according to Acute Leukemia Group B Protocol No. 7331.

Remission was never achieved and he expired following an episode of pneumonia. Autopsy findings revealed leukemic infiltration of the liver and spleen. The lungs showed right middle and lower lobe consolidation and atelectasis of the left lower lobe.

CYTOGENETIC STUDIES

Chromosome studies were performed on phytohemagglutinin (PHA)-stimulated blood and nonstimulated bone marrow by using a modified technique of Moorhead et al.[6] Skin fibroblasts were cultured in minimum essential medium supplemented with 20% calf serum. Q-banding was performed by the method of Dosik et al.[7]

Table 1 shows results of chromosome studies. Initial studies of PHA-stimulated blood, bone marrow, and skin were performed when the patient was in remission. In the bone marrow, 17 of 18 cells studied were positive for the Ph^1 chromosome and 15 of 18 cells studied showed 45 chromosomes with an absence of the Y chromosome (Fig. 1). In the peripheral blood 20 cells were

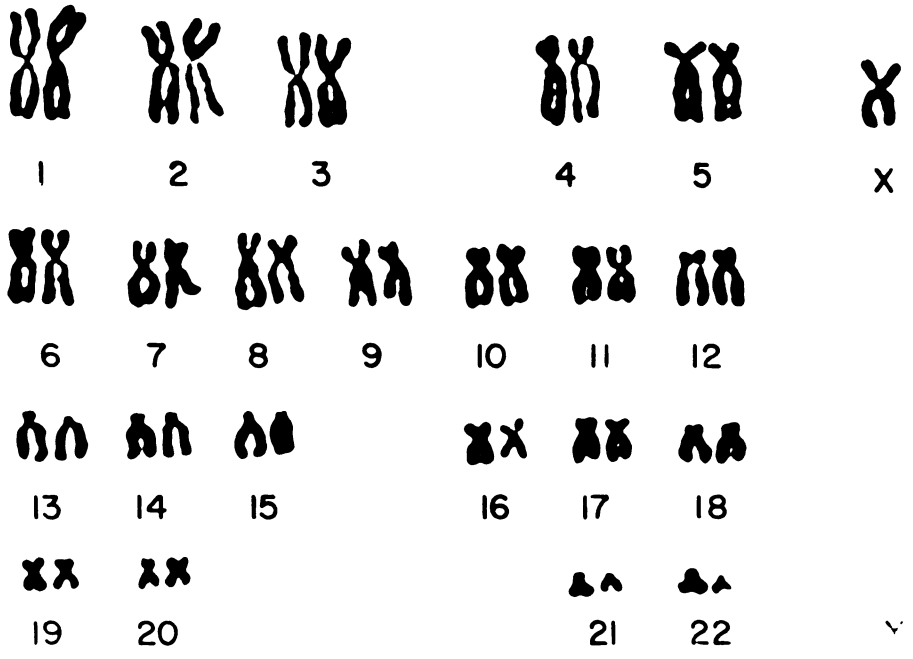

Fig. 1. Karyotype of a bone marrow cell.

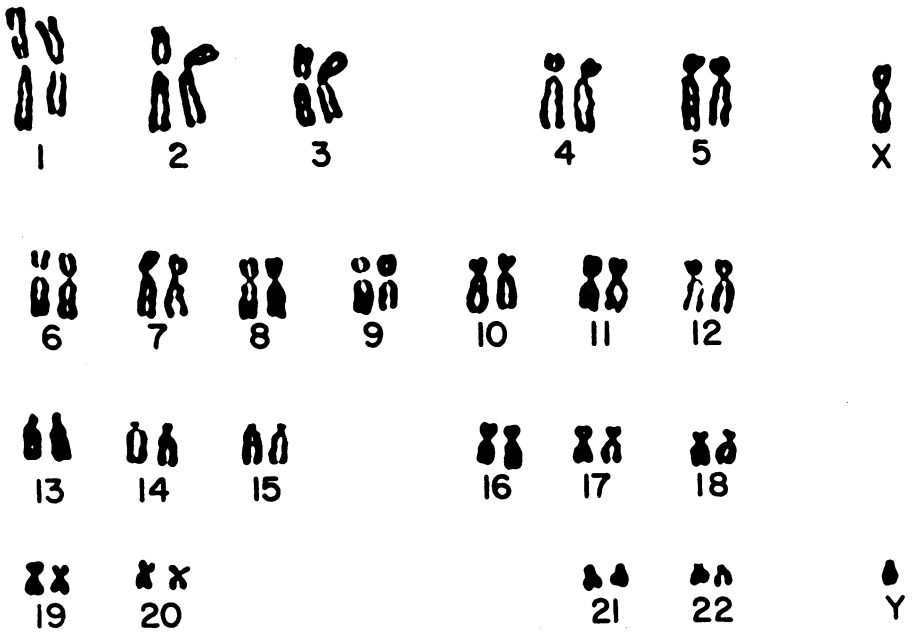

Fig. 2. Karyotype of a peripheral blood cell.

studied; 19 were of normal XY configuration (Fig. 2). Cytogenetic studies performed on skin fibroblasts were normal; 20 cells studied showed a 46 XY karyotype.

Repeat bone marrow studies during the blastic phase of the disease showed persistence of the Ph^1 chromosome in all the cells studied; 12 of 13 cells showed an absence of the Y chromosome. Q-banding confirmed the presence of the Ph^1 chromosome and the absence of the Y chromosome.

DISCUSSION

The majority of cases of CML terminate in blastic crisis, i.e., a state clinically and hematologically indistinguishable from AML. Occasionally CML can present in the blastic phase. Hammouda[8] in 1963 noted the Ph^1 chromosome in a patient with AML. The high white count, basophilia, splenomegaly, and the presence of the Ph^1 chromosome suggested the blastic phase of CML, but the short course of the disease and an increased number of blast cells were consistent with AML. The Ph^1 chromosome, although specific for CML, has been reported in exceptional cases of AML without the stigmata of CML.[2,9,10] Bornstein et al.[11] reported two cases of CML presenting in the blastic phase and reviewed the literature. They suggested that cases of AML with the Ph^1 chromosome may represent CML, without the classic phase of the disease.

Our patient's first diagnosis was AML, although hepatosplenomegaly, eosinophilia, basophilia, and the presence of myelocytes, bands, and neutrophils suggested the blastic phase of CML. Treatment with steroids for thrombocytopenia produced a rise in hemoglobin, hematocrit, and platelet count to normal levels. The white blood cell count remained elevated, but the blood and bone marrow counts were now indistinguishable from the classic phase of CML. Thus this appeared to be a remission from the blastic phase of CML. The low leukocyte

alkaline phosphatase activity, the elevated serum B_{12} levels, and the presence of the Ph^1 chromosome confirmed our clinical impression. Most previous patients with acute leukemia thought to have the blastic phase of CML have not achieved remission. The short remission phase in our patient enabled us to confirm the diagnosis of CML. It is important to distinguish the blastic phase of CML from acute leukemia for prognostic and therapeutic reasons.

Our patient had a 45 XO Ph^1 cell line in the bone marrow. Peripheral blood lymphocytes and skin culture showed a 46 XY karyotype. Atkin and Taylor[12] in 1962 described a case of CML with a 45 XO Ph^1 cell line. Since then a number of cases have been reported with this karyotype.[5,13,15,16] There are two possible reasons for the loss of the Y chromosome in our patient, i.e., either it is an age-related phenomenon or it is related to the leukemic process itself. Shiffman et al.[5] reported two cases of CML with a 45 XO Ph^1 cell line and reviewed the literature. In 21 cases, the age range was 27–72 yr. Seven patients were above 58; age was not reported in three patients. A 45 XO karyotype in hematologically normal males of 56–94 yr has been reported by Pierre and Hoagland[17] and O'Riordon et al.[18] The age range was lower for CML than normals and although our patient was 58 yr old, it would seem likely that the leukemic process itself was responsible for the loss of the Y chromosome. Additional evidence supporting this hypothesis was reported by Sellyei and Vass[19] and Zenkel et al.[20] They reported the loss of the Y chromosome from tumor cells in many cases of meningioma and lung cancer.

Garson and Milligan[13] and Sanberg and Skurai[14] have suggested that absence of the Y chromosome may prevent the development of the blastic phase of CML and their findings are quoted by Wintrobe.[21] Reports to the contrary have already appeared in the literature,[5,15,16] and our case presented in the blastic phase. This finding would suggest that the absence of the Y chromosome in patients with CML is not beneficial.

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