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CASE REPORT

Acute Lymphoblastic Leukemia Followed by Chronic Myelocytic Leukemia

By Giovanna Tosato, Jacqueline Whang-Peng, Arthur S. Levine, and David G. Poplack

Second hematologic malignancies occur rarely in patients previously treated for leukemia. This report describes a patient with acute lymphoblastic leukemia who remained in complete remission for 5 yr and then developed chronic myelocytic leukemia (CML). The original lymphoblasts were associated with a partial deletion of chromosome 21, while CML was associated with a classic Philadelphia marker, indicating the independent origin of the two leukemias.

THE DEVELOPMENT of a second hematologic malignancy is a rare event. However, several cases of Ph[1]-positive chronic myelocytic leukemia (CML) have been reported in patients with previously diagnosed chronic lymphocytic leukemia (CLL), Hodgkin disease, and non-Hodgkin lymphoma.

In this report we describe a patient with acute lymphoblastic leukemia (ALL) who developed a Ph[1]-positive CML after 5 yr in continuous remission. The occurrence of different chromosomal patterns with each leukemia suggests an independent clonal origin.

MATERIALS AND METHODS

Chromosome preparations of the mitotic cells in the bone marrow were studied without prior culture in vitro as previously described.[1] Peripheral blood was cultured for 24 and 72 hr with or without phytohemagglutinin (PHA) stimulation, and preparations were made according to the technique of Moorhead et al.[2] A modification of the trypsin-Giemsa banding technique as described by Seabright was used.[3] The cells in metaphase were scored, analyzed, and karyotyped according to the criteria defined at the Paris conference.[4] Peripheral blood and bone marrow aspirate smears were examined as previously described.[5]

CASE REPORT

A 30-yr-old female was referred to the National Cancer Institute in January 1972 with the diagnosis of ALL. She had experienced mild shortness of breath and bone pain for a period of 6 mo prior to admission. Physical examination was unremarkable. Admission blood counts showed a WBC of 5.7×10^9/liter of which 5% were lymphoblasts, Hb 8.9 g/dl, and platelet count 100×10^9/liter. The bone marrow showed total replacement with leukemic lymphoblasts. Peroxidase staining was negative, and PAS reaction was coarsely positive in 5% of the blasts. The remainder of the laboratory findings was normal except for a lactic dehydrogenase of 2200 U/liter.

Chromosomal analysis of the bone marrow revealed the presence of a Ph[1]-like chromosome in the majority of leukemic cells (Fig. 1). This was identified by the trypsin-banding technique as a 21q- chromosome; the karyotype was thus 46,XX,21q-. Treatment was initiated with L-aspa-

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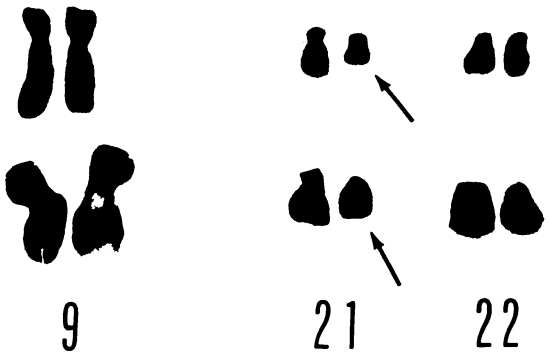

Fig. 1. Partial karyotypes showing chromosomes 9, 21q-, and 22. Top row, conventional Giemsa stain. Bottom row, Giemsa-trypsin banding.

raginase, vincristine, and prednisone, and after 3 wk the patient achieved a marrow remission. She received central nervous system prophylaxis with intrathecal methotrexate and maintenance chemotherapy with methotrexate and 6-mercaptopurine; maintenance was continued for 3.5 yr until August 1975, when chemotherapy was discontinued. Followup cytogenetic analyses performed on remission marrows showed normal chromosomal patterns in 1973 and 1975, but in 1976, 4 yr after ALL was diagnosed, the 21q- marker was again observed in 5% of bone marrow metaphases.

The patient remained in complete remission for 5 yr following the diagnosis of ALL. In January 1977, progressive granulocytosis, thrombocytosis, and bone marrow myeloid hyperplasia were noted. The patient was asymptomatic, and physical examination was unremarkable. Because of its known bone marrow stimulatory effects, lithium, which the patient had been taking as an antidepressant for the previous 2 yr, was discontinued. The patient was followed closely, and in August 1977 a leukocytosis of 90×10^9/liter was noted. The differential count showed 32% polys, 21% bands, 15% metamyelocytes, 25% myelocytes, 5% lymphocytes, and 2% monocytes. The hemoglobin was 12 g/dl and the platelet count 600×10^9/liter. Bone marrow examination showed hypercellularity with a pronounced myeloid hyperplasia. Serum vitamin B_{12} was 2400 ng/liter; however, leukocyte alkaline phosphatase, lactic dehydrogenase, and fetal hemoglobin were normal. Chromosomal analysis of the bone marrow now showed a classical Ph^1 chromosome, with a karyotype of 46,XX,t(9;22)(q34;q12) by Giemsa-trypsin banding (Fig. 2).

The diagnosis of CML was made and treatment with busulfan was begun. Within 4 wk the white cell count fell to 10×10^9/liter, the platelet count and the hemoglobin were within the normal range, and the bone marrow continued to show granulocytic hyperplasia. At this writing (8 mo later) the patient continues on chemotherapy with busulfan and is clinically and hematologically stable.

DISCUSSION

We described a patient with ALL who developed CML after 5 yr of continuous complete remission. Cytogenetic analysis showed that separate chromosomal markers characterized the two leukemias. The chromosome marker 21q- was present in virtually all bone marrow metaphases when ALL was diagnosed and was demonstrable in 5% of the bone marrow cells 4 yr later while the patient was still in complete remission. However, when CML developed, no 21q- marker could be identified, and the Ph^1 chromosome was present in virtually all bone marrow and peripheral blood metaphases.

Chromosomal abnormalities are frequently found in ALL.[6-8] These abnormal genotypes may persist throughout remission and are not invariably associated with future relapse.[7,8] While the etiology and significance of these "silent" chromosome abnormalities during remission is unclear, they do suggest the persistence of a malignant clone.

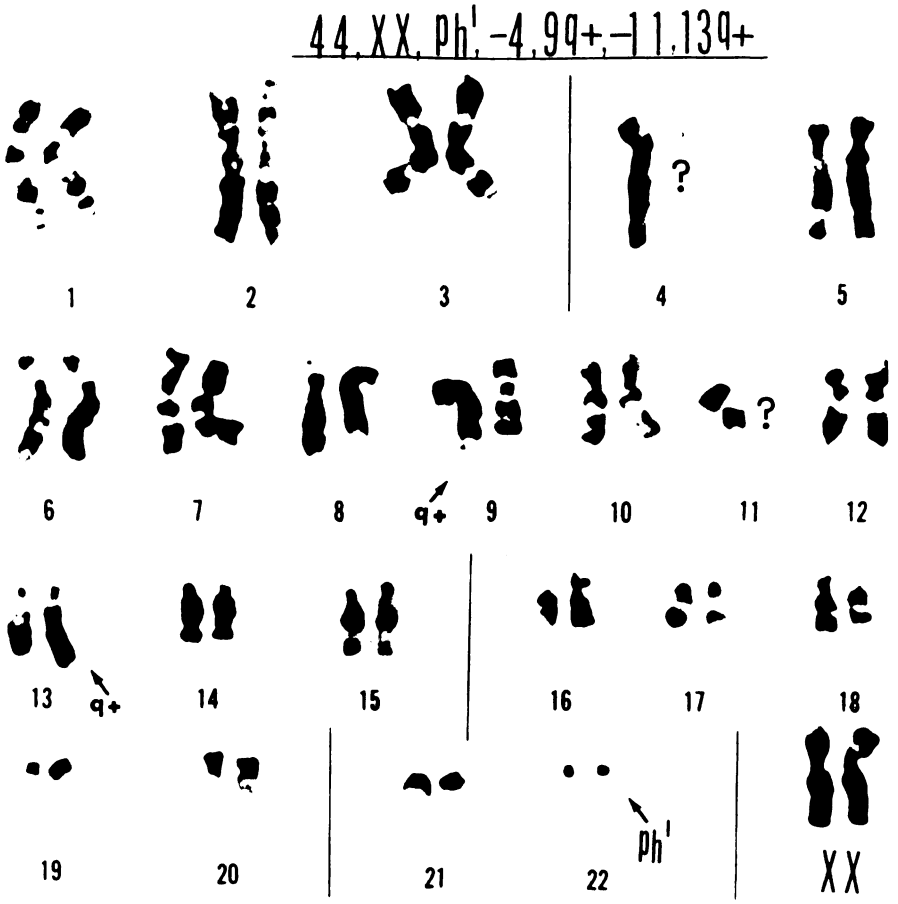

Fig. 2. 46,XX karyotype with the typical Ph¹ translocation to chromosome 9 [t(9;22)(q34;q12)]. Giemsa-trypsin banding.

The development of a new chromosome marker, concomitant with a morphologic change to CML, strongly suggests that the patient described in this report developed a new malignant cellular clone and a second leukemia. Second leukemias have been previously reported but appear to be a rare event.[9 15] Several hypothesis have been advanced to explain this phenomenon: persistence of the original "leukemogenic factor," impairment of the patient's immune surveillance system, or the effects of therapeutic modalities such as radiation and/or cytotoxic therapy.[16] It is intriguing that this patient had been receiving lithium salts, known to stimulate granulocyte production,[17,18] for 2.5 yr prior to the development of CML.

A significant number of patients with CML present initially with a lymphoid blast crisis or develop such an event during the course of their disease.[19 22] Since these lymphoid blasts are morphologically identical to ALL cells,[23] chromosomal analysis is helpful in establishing the correct diagnosis. The patient described in this report presented with ALL and 5 yr later developed a Ph¹ chromosome-positive CML. The availability of chromosomal analysis allowed

us to establish the independent nature of these two leukemias. This case emphasizes the importance of performing chromosomal analyses on all patients with leukemic processes.

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