Karyotypic Polymorphism in Acute Myelofibrosis

By Ila Shah, Kazutoshi Mayeda, Fred Kopitch, Sayed Mahmood, and Barbara Nemitz

Acute myelofibrosis (AMF) was diagnosed in a 59-yr-old black male in September 1978, on the basis of pancytopenia, lack of hepatosplenomegaly, fibrosis of the marrow, and paucity of teardrop red blood cells in the peripheral blood. Since then the patient has demonstrated an unusually long survival of 36 mo with a changing cytogenetic course. His initial karyotype of 46 XY normal karyotype changed in 20 mo to trisomy 8. Followed 1 yr later by 1:4 translocation in peripheral blood. Simultaneously with these changes, the patient had a chronic anemia, lack of hepatosplenomegaly, fibrosis of the bone marrow, and platelet count of 17,000/cu mm. A new clone of 1:4 translocation was later detected in the peripheral blood.

Acute myelofibrosis is a relatively new entity described originally by Lewis and Szur in 1963 and since reported by many investigators. It is characterized by pancytopenia, minimal anisopoikilocytosis, minimal splenomegaly, and a rapidly progressive course. Some of the chromosomal abnormalities associated with acute myelofibrosis are trisomy 8, anisopoikilocytosis, minimal splenomegaly, and a rapidly progressive course. It is characterized by pancytopenia, minimal anisopoikilocytosis, minimal splenomegaly, and a rapidly progressive course. Some of the chromosomal abnormalities associated with acute myelofibrosis are trisomy 8, anisopoikilocytosis, minimal splenomegaly, and a rapidly progressive course.

CASE REPORT

N.E., a 59-yr-old black male, was seen originally in September 1978 for weakness, dizziness, and easy bruising of 2 wk duration. His past medical history was unremarkable. There was no history of exposure to radiation or cytotoxic therapy. Physical examination was significant for extreme pallor, ecchymoses, petechiae, a grade II/VI systolic murmur and a barely palpable spleen. Initial laboratory examination showed hemoglobin 4.5 g/dl, hematocrit 15%, WBC 4200/cu mm with 24% PMNs, 6% bands, 5% myelocytes, 10% promyelocytes, 12 positive myelocytes, and 8% myeloblasts. His peripheral smear demonstrated target cells, an absolute lack of nucleated RBCs, and a hemoglobin of 3.5 g/dl platelet count 32,000/cu mm. A repeat bone marrow aspiration and biopsy of the core showed hypocellular marrow with extreme myeloid hyperplasia and near total absence of fibrosis, confirmed by trichrome and reticulin stains. Because of the very high white blood count, the patient was treated with oral hydroxyurea, 2 g daily, and transfusions of packed RBCs. His white blood count responded with a drop to 36,000/cu mm in 3 days. His platelet count was stable at a range of 57-75,000/cu mm. The cytogenetic studies at this time showed a reversal to normal 46, XY karyotype, both in the bone marrow and in the peripheral blood.

MATERIALS AND METHODS

Chromosome Studies

Bone marrow samples were collected in heparinized syringes. All of the bone marrow samples were harvested directly by the method of Hozier et al. and colcemided for 20 min. Representative metaphases were selected under phase contrast and stained with quinacrine mustard dihydrochloride (Sigma, St. Louis, Mo) using a modified method of Casperson et al. A Zeiss photomicroscope II was used for photomicroscopy. At least 35 metaphases were examined from each specimen.

Peripheral blood lymphocytes were stimulated with phytohemagglutinin (GIBCO, Grand Island, N.Y.), cultured for 72 hr in...
RPMI-1640 (GIBCO), and colcemided for 20 min. Specimens were harvested according to a modification of Moorhead et al.14 Photomicroscopy was the same as that previously described for bone marrows.

### DISCUSSION

Myelofibrosis with agnogenic myeloid metaplasia is a disorder characterized by chronic course, prominent hepatosplenomegaly, and striking teardrop poikilocytosis. The bone marrow may be hypercellular in the early stages, but usually becomes fibrotic in the end, with replacement of all the hematopoietic tissue. Acute myelofibrosis (AMF), on the other hand, has been recognized as a separate entity. The original description was by Lewis and Szur in 1963. Various authors have since described this entity as malignant myelosclerosis, acute agnogenic myeloid metaplasia (AAMM), acute myelofibrosis, or acute megakaryoblastic leukemia.25

Bearman et al. attempted to formulate strict criteria for the diagnosis. These include: (1) pancytopenia at the time of presentation; (2) minimal aniso and poikilocytosis; (3) minimal to absent splenomegaly; (4) hypercellular marrow with fibrosis; and (5) increase in reticulin fiber content. By strict application of these criteria, three-fourths of the cases described in the literature could not be termed acute myelofibrosis.

In addition, myelofibrosis can be seen in the preterminal or accelerated phase of polycythemia rubra vera and chronic granulocytic leukemia. However, as seen in this patient, the transformation from severe myelofibrosis into chronic granulocytic leukemia is most unusual. The course usually observed is the transformation into acute granulocytic leukemia, with a very short survival.

Cytogenetic studies in myelofibrosis reveal aneuploidy in 60%–70% of cases,8 and C-D translocations with marker chromosomes appear to be common.9 Nowell et al. studied two patients with acute myelofibrosis, both of whom demonstrated trisomy 8 in myeloblasts.10 Bartoli et al. have also described trisomy 8 in a patient with acute myeloid metaplasia (AAMM). However, Nowell et al. did not attach preleukemic significance to the development of trisomy 8 in these patients. Den Ottolander et al. have described trisomy 10 in one patient.13 Van Slyck et al. have described a 1:3 translocation in myelofibrosis with absence of this finding in fibroblasts, indicating a secondary role for fibrosis.11

Our patient demonstrated a spectrum of cytogenetic abnormalities over a period of 3 yr. Starting from a normal karyotype in 1978 (Fig. 1), he changed to

Table 1. Cytogenetic Findings in the Bone Marrow and Peripheral Blood Over 3 Yr

<table>
<thead>
<tr>
<th>Date</th>
<th>Bone Marrow (%) Metaphases</th>
<th>Peripheral Blood (%) Metaphases</th>
</tr>
</thead>
<tbody>
<tr>
<td>9/78</td>
<td>Not obtained</td>
<td>46, XY (100%)</td>
</tr>
<tr>
<td>11/79</td>
<td>46, XY (100%)</td>
<td>46, XY (100%)</td>
</tr>
<tr>
<td>5/80</td>
<td>47, XY, +8 (4%)</td>
<td>46, XY (100%)</td>
</tr>
<tr>
<td>11/80</td>
<td>47, XY, +8 (50%)</td>
<td>47, XY, +8 (10%)</td>
</tr>
<tr>
<td>2/81</td>
<td>47, XY, +8 (27%)</td>
<td>47, XY, +8 (15%)</td>
</tr>
<tr>
<td>5/81</td>
<td>46, XY (100%)</td>
<td>46, XY, t(1:4)(p32;q35) (6%)</td>
</tr>
<tr>
<td>8/81</td>
<td>46, XY (100%)</td>
<td>46, XY (100%)</td>
</tr>
</tbody>
</table>
trisomy 8 (Fig. 2), followed by 1:4 translocation (Fig. 3) in the peripheral blood, which then led to clinical development of a leukemic picture. It is notable that the patient reverted to a normal 46, XY karyotype in the bone marrow prior to the appearance of 1:4 translocation in the peripheral blood, and subsequently normal karyotype was seen in the peripheral blood.

We present this case because of the following unusual features. (1) Our patient fits the criteria for acute myelofibrosis (AMF) at the time of initial diagnosis, but has since demonstrated an unusually long survival. (2) He has demonstrated a transition consecutively from a normal 46, XY karyotype to trisomy 8, to 1:4 translocation and then back to 46, XY karyotype, perhaps indicating simultaneous presence of multiple clones. (3) Absence of cytogenetic abnormality in the fibroblasts and the near absence of fibrosis at the end confirm the secondary role of fibrosis.
REFERENCES

Karyotypic polymorphism in acute myelofibrosis

I Shah, K Mayeda, F Koppitch, S Mahmood and B Nemitz

Updated information and services can be found at: http://www.bloodjournal.org/content/60/4/841.full.html
Articles on similar topics can be found in the following Blood collections

Information about reproducing this article in parts or in its entirety may be found online at: http://www.bloodjournal.org/site/misc/rights.xhtml#repub_requests

Information about ordering reprints may be found online at: http://www.bloodjournal.org/site/misc/rights.xhtml#reprints

Information about subscriptions and ASH membership may be found online at: http://www.bloodjournal.org/site/subscriptions/index.xhtml