Association of the Translocation (15;17) With Malignant Proliferation of Promyelocytes in Acute Leukemia and Chronic Myelogenous Leukemia at Blastic Crisis

By Shinichi Misawa, Edward Lee, Charles A. Schiffer, Zemin Liu, and Joseph R. Testa

Cytogenetic studies were performed on nine patients with acute promyelocytic leukemia. Every patient had an identical translocation (15;17) or, in one case, a variant three-way rearrangement between chromosomes 7, 15, and 17. Another patient with chronic myelogenous leukemia was examined at the time of blastic crisis when the patient’s bone marrow was infiltrated by hypergranular promyelocytes and blasts. Bone marrow cells contained a t(15;17) as well as a Ph' chromosome. Only the latter abnormality was observed in the chronic phase of the disease. The translocation (15;17) was detected in all ten patients when bone marrow or peripheral blood cells were cultured for 24 hours prior to making chromosome preparations. However, the t(15;17) was not seen in three of these same cases when bone marrow cells were processed directly. These findings indicate that the t(15;17) is closely associated with acute proliferation of leukemic promyelocytes and that detection of this karyotypic defect may be influenced by the particular cytogenetic processing method used in different laboratories. An analysis of the banding pattern in the variant translocation provided additional evidence favoring chromosomal breakpoints at or very near the junction between bands 17q12 and 17q21 and at 15q22.

RESULTS

Eight patients with APL showed a specific translocation between chromosomes 15 and 17, t(15;17)(q22;q11) or q12 (Fig 1a–c). The remaining patient with APL (case 580) had a variant form of this translocation involving chromosomes 15, 17, and 7, t(7;17)(p22;q21.1) or q12q22) (Fig 2a and b). The t(15;17) was seen as the sole abnormality in five patients, whereas this rearrangement was accompanied by other karyotypic changes in four others. In the latter group, a gain of chromosome 8 was observed in two cases, a deletion of 6q in one case, and an inversion of chromosome 20 in one case (Table 2).

The patient with CML blastic crisis had a t(15;17) superimposed upon a Ph'-translocation, t(9;22)(q34;q11), in most marrow cells examined. Among ten cells analyzed at the time of blastic crisis, four showed only a Ph', four had a t(15;17) accompanying a Ph' (Fig 2c), and two cells showed a missing Y chromosome as well as a t(15;17) and a Ph'. Chromosome preparations of bone marrow cells at the time of diagnosis were inadequate for analysis. However, pokeweed mitogen-stimulated mononuclear cells from peripheral blood revealed a standard Ph' translocation as the sole abnormality in 16 of 24 cells at diagnosis; the eight remain-
Peripheral Blood Bone Marrow

Table 1. Clinical and Hematologic Findings in Nine Patients With APL and One Patient With Promyelocytic Blastic Crisis of CML

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Case No.</th>
<th>Age/Sex</th>
<th>Diagnosis</th>
<th>WBC (x 10^9/L)</th>
<th>Blasts (%)</th>
<th>Promyelocytes (%)</th>
<th>Blasts (%)</th>
<th>Promyelocytes (%)</th>
<th>DIC</th>
<th>Chemotherapy Response (months)</th>
<th>Survival† (months)</th>
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<tr>
<td>181</td>
<td>32/F</td>
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<td>64.6</td>
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<td>40</td>
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<td>20.4</td>
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<td>40</td>
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<td>DNR, AC CR</td>
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</tr>
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<td>2.0</td>
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<td>DNR, AC CR</td>
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<td>47</td>
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<td>24</td>
<td>34</td>
<td>yes</td>
<td>AZQ CR</td>
<td>none 1(26)</td>
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Abbreviations: DIC, disseminated intravascular coagulation; DNR, daunorubicin; AC, arabinofuranosil cytosine; CR, complete remission; AZQ, aziridinylbenzoquinone.

*Patients were examined cytogenetically at the time of diagnosis of APL except for those marked with (‡) or (§), in which case the cytogenetic study was done in relapse of APL (‡) or at the time of blastic crisis of CML (§).

†Survival is from the time of diagnosis of APL or, in case 545, from the onset of promyelocytic blastic crisis. Number in parentheses in case 545 is the survival from the initial diagnosis of chronic-phase CML. (+), alive as of January 1, 1985. Two patients remain in initial complete remission; patient 547 recently relapsed after a CR of 12 months' duration.

Table 2. Cytogenetic Findings of Nine Patients with APL and One Patient With Promyelocytic Blastic Crisis of CML

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Case No.</th>
<th>Sample Source</th>
<th>Karyotype</th>
<th>No. of Metaphase Cells Analyzed†</th>
<th>Direct</th>
<th>24-hr</th>
<th>MTX</th>
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<td>248</td>
<td>BM</td>
<td>46,XY(t;15;17)</td>
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<td>5</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>282</td>
<td>BM</td>
<td>46,XY(t;15;17)</td>
<td></td>
<td>13</td>
<td>5</td>
<td>2</td>
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</tr>
<tr>
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<td>PB</td>
<td>46,XY(t;15;17)</td>
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<td>13</td>
<td>5</td>
<td>2</td>
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<tr>
<td>547</td>
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<td>46,XY(t;15;17)</td>
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<tr>
<td>552‡</td>
<td>BM</td>
<td>46,XY(t;15;17)</td>
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</tbody>
</table>

Abbreviations: BM, Bone marrow; PB, peripheral blood without mitogen stimulation.

*Patients were examined cytogenetically at the time of diagnosis of APL except for those marked with (‡) or (§), in which case the cytogenetic study was done in relapse of APL (‡) or at the time of blastic crisis of CML (§).

†Number of banded mitoses examined. Direct, direct sample; 24-hour, 24-hour culture without synchronization; MTX, methotrexate-synchronized culture.

DISCUSSION

All nine patients with APL had a standard or variant translocation (15;17). Among approximately 100 acute leukemia patients studied at our center, this rearrangement was...

Fig 1. Partial Q-banded (A, B) and G-banded (C) karyotypes showing a 15;17 translocation, t(15;17)(q22;q21.1 or q12), from cases 242(A), 248(B), and 638(C). Arrows indicate possible breakpoints in the defective chromosomes.
Fig 2. Partial Q-banded karyotypes showing a t(7;17;15)(p22;q21.1 or q12;q22) from case 580(A,B), and a t(15;17) and a t(9;22)(q34;q11) from case 545(C). Arrows indicate proposed breakpoints in the defective chromosomes.

not observed in any other type of acute leukemia. Since the first report of a t(15;17) in APL, this abnormality has consistently been associated with this disease type. The incidence of APL patients with a t(15;17) has differed considerably from one institution to the next, and an unusual geographic distribution of APL cases with the t(15;17) has been noted. For example, the t(15;17) was observed in 27 of 27 patients in Chicago, in 12 of 12 patients in Sapporo, Japan, but in none of 12 patients in Finland and Sweden. It is now recognized that the t(15;17) may be found in a higher percentage of cells in cultured material than in the direct specimen, and in some cases the t(15;17) could be detected only in cultured samples, as in three of our cases. The reason for the difference in the incidence of chromosome abnormalities between direct and cultured preparations remains to be elucidated. However, Berger et al suggested that mitotic cells in the direct preparations are more likely to be normal erythroblasts, whereas mitotic cells in the cultured specimen are more likely to be leukemic cells since a decrease in normal metaphases in the culture coincides with the disappearance of dividing erythroblasts.

Two additional patients with clinical characteristics suggestive of APL, including the presence of DIC, were seen during the same time period of this study. One patient showed light to moderate granulation in some blasts and was classified morphologically as having M2 leukemia both by light and electron microscopy. Chromosomal banding analysis of 24-hour bone marrow cultures at diagnosis and relapse failed to reveal any karyotypic defects. The other patient was a 27-year-old male with CML blastic crisis; 15% to 20% of circulating and marrow blasts were heavily granulated. Cytogenetic studies revealed a mosaic karyotype: 46,XY, t(9;22)/46,XY,t(8;10),t(9;22)/49,XY,+6,+8p+,+13, t(8;10),t(9;22). Auer’s rods could not be identified in either patient. Thus, available evidence suggests that the t(15;17) is highly specific for acute proliferation of leukemic promyelocytes, but DIC and the presence of some cells with increased granulation are not necessarily associated with this translocation.

Four of our cases showed chromosomal changes in addition to the t(15;17). A gain of chromosome 8 was detected in two patients, which is not an uncommon finding in APL. Furthermore, a +8 is a karyotypic change commonly seen in patients with various types of acute nonlymphocytic leukemia (ANLL), with no specificity for a certain type of ANLL.

Even though one of our patients showed a complex three-way translocation, the breakpoints in chromosomes 15 and 17 appeared to be at the same bands involved in the standard t(15;17). Previously, Bernstein et al reported two other cases of complex 15;17 translocations in which chromosomes 15, 17, and either chromosome 2 or 3 were involved. More recently, Ohyashiki et al described a complex four-way translocation (involving chromosomes 1, 5, 15, and 17) in another patient with APL. In all of these cases there is a translocation of the distal part of the long arm of chromosome 17 to the long arm of chromosome 15 and of the distal portion of the long arm of chromosome 15 to a chromosome other than 17. In each case, a characteristic 15q+ abnormality is generated.

Three variant simple translocations have also been described in APL. In these cases, the distal portion of 17q was thought to be translocated to either chromosome 1, 7, or 8, without involvement of chromosome 15. However, bone marrow chromosomes often show ill-defined bands in APL, and it is possible that the 15q+ exists in these cases but has been called a chromosome 14.

There has been considerable confusion with regard to the
precise location of the breakpoints in the t(15;17) (for review, see ref 19). The marrow chromosomes obtained from patients with APL are often contracted, and this makes difficult exact delineation of the break sites.20 Hagemeijer et al21 and Larson et al5 have examined extended chromosome preparations from patients with the t(15;17), and breakpoints at 15q22 and 17q12 or 17q21.1 were proposed.21 Genetic analysis of the t(15;17) using somatic cell hybridization technology yielded results compatible with this interpretation.22 The banding in our patients with the standard t(15;17) was also consistent with such a proposal. Moreover, the variant rearrangement seen in one of our patients provided us with the opportunity to examine the defective chromosome 17 without the usual translocation of bands from chromosome 15. In this complex rearrangement 15q22 → 15pter is translocated to chromosome 7 at band 7p22. The derivative 7 retains the medium fluorescent Q band 7p21, and only part of the tiny, weakly fluorescent terminal band (7p22) may be transposed to the derivative 17 chromosome (17q→). The pale fluorescent band retained on the long arm of the 17q→ seems to represent all or most of band 17q12. Thus, the banding in the variant translocation appears to provide additional evidence favoring breakpoints at or very near the junction between 17q12 and 17q21 and at 15q22. Dayton et al proposed that the cellular oncogene c-erbA may have a role in the development of APL because of its apparent close proximity to the chromosome 17 breakpoint associated with this disease.23 They assigned c-erbA to the q21-22 region of chromosome 17 and provided evidence that the c-erbA sequences remain on the 17q→ chromosome in APL cells. Therefore, the genetic and karyotypic results, taken together, suggest a breakpoint in the proximal end of band q21(q21.1) of chromosome 17. Rowley has proposed that in APL the 15q+ is the constant recombinant and the critical gene rearrangement leading to malignant transformation is related to the movement of the end of 17q to 15q++.24 Since c-erbA apparently is retained on the defective 17 and is not located near the conserved junction on the 15q+, this oncogene may have nothing to do with the disease.

Our patient 545 is the second reported case of a t(15;17) in a promyelocytic form of blastic crisis in CML. The first case was described by Berger et al.25 Their patient had a chronic phase of 8 months' duration during which time the marrow showed only a Ph1 translocation. The patient developed promyelocytic blast crisis with a t(15;17) superimposed upon the Ph1 cell line. The t(15;17) disappeared from the bone marrow after chemotherapy. The findings in these two cases imply that the translocation (15;17) has an important role in acute malignant proliferation of promyelocytes even in CML cells that already have a specific structural aberration, t(9;22), and are committed to proliferate into granulocytes, erythrocytes, and megakaryocytes.26 Recently, Moir et al reported a case of acute myelomonocytic leukemia with an increase of eosinophils, basophils, and hypergranular promyelocytes, the latter occasionally showing bundles of Auer rods.27 Chromosomal studies revealed an inv(16)(p13q22) in 27 of 30 cells. Furthermore, seven of these karyotypically abnormal cells showed a t(15;17) in addition to the inv(16). The appearance of the t(15;17) in association with an increase of abnormal promyelocytes suggested that acute promyelocytic transformation occurred during the course of acute myelomonocytic leukemia. Thus, these observations provide additional evidence for the specificity of certain chromosomal rearrangements for particular target cells. The association of a t(15;17) with a specific cell (i.e., malignant promyelocytes), even when the clinical diagnosis is different, suggests that the altered chromosomes carry genes important to the function, maturation, and/or proliferation of this cell.

REFERENCES

16. Ohayashi K, Oshima K, Uchida H, Nomoto S, Sakai N,


Association of the translocation (15;17) with malignant proliferation of promyelocytes in acute leukemia and chronic myelogenous leukemia at blastic crisis

S Misawa, E Lee, CA Schiffer, Z Liu and JR Testa