To the editor:

**Chromosome 19 abnormalities are commonly seen in AML, M7**

A recent paper by Dastugue et al1 reported the cytogenetic profile of 53 patients with acute megakaryoblastic leukemia (FAB-M7). The authors studied 30 children and 23 adults evaluated by the Groupe Français de Cytogénétique Hématologique, and identified 9 different groups based on their conventional cytogenetic analysis. These groups reflect, in part, the known association of M7 leukemia with Down syndrome, with the t(1;22) translocation, 3q21 or q26 translocations, and with the Philadelphia chromosome [t(9;22)]. No new recurrent abnormalities were identified, although mapping of breakpoints identified possible rearrangement hot spots involving 17q, 11q, 21q, and 16q. Table 1 in their manuscript showed 7 patients with trisomy 19, 1 patient with a hyperdiploid karyotype and an extra copy of chromosome 19, 1 patient with loss of 19, 1 patient with add(19)(p13), and 1 patient with a t(4;19) (p12?) translocation.

In 2001, we reported the frequent gain of chromosome 19 in megakaryoblastic leukemias using comparative genomic hybridization (CGH).2 We used CGH and G banding to analyze both primary patient samples and megakaryoblastic cell lines, and we found chromosome 19 abnormalities in 4 patients by CGH that we could not identify by G banding. Four of 12 patient samples analyzed demonstrated trisomy 19 (+19q13), with 2 of 4 acute megakaryoblastic leukemia–M7s (AML-M7s) and 2 of 8 secondary acute leukemias, which occurred after a myeloproliferative disorder, demonstrating this abnormality. In addition, 9 of the 11 megakaryocytic leukemia cell lines that we analyzed showed gain of 19 or +19q by CGH.

The larger study by Dastugue et al identified an approximately 20% incidence of chromosome 19 abnormalities with trisomy 19 occurring in 8 (16%) of 50 patients lacking the Philadelphia chromosome. The presence of this abnormality in 8 of 9 cytogenetic subgroups suggests its commonality in this disease process. Little emphasis was placed on this finding in their discussion and our studies suggest that the true incidence of trisomy (or amplification) of chromosome 19 could be even higher, if more sensitive studies such as comparative genomic hybridization or spectral karyotyping (SKY) are performed. This may be especially true in the adult group, as 6 (26%) of 23 adult patients had marker chromosomes, which could contain chromosome 19 material, as we found to be the case in the M7 cell lines that we analyzed.

The 19q13 region is gene rich and includes the AKT2, cyclin E, and MLL2 genes, among others. These particular candidate genes have been implicated in solid tumors and are under investigation in hematologic malignancies as well. We believe the Dastugue study provides further support for investigating the role of chromosome 19 abnormalities in the megakaryoblastic leukemias.

Stephen D. Nimer, Donal MacGrogan, Suresh Jhanwar, and Sara Alvarez

Correspondence: Stephen D. Nimer, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY 10021; e-mail: s-nimer@mskcc.org

**References**

nonrandom abnormalities characterizing the megakaryoblastic proliferations.

References


To the editor:

Deficiency of ADAMTS13 and thrombotic thrombocytopenic purpura

Bianchi et al report a severe deficiency of the von Willebrand factor (VWF)-cleaving protease ADAMTS13 is specific for thrombotic thrombocytopenic purpura (TTP). This is in agreement with the results of our studies, demonstrating that a severe deficiency of ADAMTS13 is detected only in patients with either the acquired or congenital form of TTP but not in patients with other pathologic conditions. On the other hand, Remuzzi et al report contradictory results. Discrepancy in the case criteria clearly contributes to the variant results observed by Remuzzi et al. The syndrome of thrombocytopenia and microangiopathic hemolysis consists of a heterogeneous group of disorders with overlapping clinical manifestations but different pathogenesis. In the study by Remuzzi et al, criteria for distinguishing TTP from hemolytic uremic syndrome (HUS), based on the presence of neurologic or renal abnormalities, are unfortunately arbitrary. The use of a decreased high-molecular-weight (HMW) multimers to low-molecular-weight (LMW) multimers ratio (HMW/LMW) as an indicator of increased cleavage of VWF is particularly misleading because VWF multimer size distribution is determined by a kinetic balance among secretion, proteolysis, and VWF-platelet binding. At the advanced stage of TTP, VWF-platelet binding predominates, resulting in a depletion of the ultralarge and large multimers; hence, a normal or even decreased HMW/LMW-multimer ratio is common, as observed by Remuzzi et al. Now that the molecular mechanism of TTP is elucidated, it would be of little value and counterproductive to apply the diagnosis of TTP to patients who do not have severe ADAMTS13 deficiency. A deficiency of ADAMTS13 as the cause of the manifestations of TTP offers an explanation of why plasma infusion or exchange is effective. The role of plasma therapy in patients without deficiency of ADAMTS13 is questionable. Since plasma exchange is costly and associated with potentially serious complications, efforts should be directed toward delineating the role, if any, of plasma therapy in patients without TTP.

Bianchi et al also report that ADAMTS13 activity is very low in some cases with heparin-induced thrombocytopenia or severe sepsis, and they raise doubt that all cases of TTP are associated with a severe deficiency of ADAMTS13 activity. First, in patients with heparin-induced thrombocytopenia, the ADAMTS13 activity is not as low as the authors report. Previously, we investigated the level of ADAMTS13 activity in 18 patients with heparin-induced thrombocytopenia. Table 1 compares the result of that study with that described by Bianchi et al. While 4 of our cases had ADAMTS13 activity below the normal range, none had a level below 30%. The discrepancy is obviously due to the difference in the normal ranges of the assays. Notably, the narrow normal range of our assay is critical for correctly identifying the members in kindreds with genetic deficiency of the protease, leading to the positional cloning of the ADAMTS13 gene.

Furthermore, the low levels of ADAMTS13 detected by Bianchi et al in patients without TTP are not accompanied by evidence that cleavage of VWF is diminished. Since ADAMTS13 regulates the size of VWF in the circulation, a low ADAMTS13 level that is not associated with evidence of diminished VWF cleavage raises doubt on the validity of the test result. Alternative explanations of low laboratory values, such as plasma factors interfering the assays or instability of ADAMTS13 activity in vitro, have not been explored. Hence, unless the result is supported by evidence of diminished VWF proteolysis or the presence of inhibitors, we urge caution before inferring that a low laboratory value indicates that the ADAMTS13 activity is decreased in the patient.

On the other hand, clinical observations and laboratory studies suggest that in conditions with severe ADAMTS13 deficiency, the propensity of VWF to bind platelets is likely to be affected by the genetic composition of the individuals and by environmental factors such as fever, infection, surgery, or pregnancy. Just as patients with von Willebrand disease have variable severity of bleeding manifestations, in patients with severe ADAMTS13 deficiency, the absence of apparent thrombocytopenia or microangiopathic hemolysis is not evidence against the diagnosis of TTP, provided the low level of ADAMTS13 is supported by evidence of decreased VWF proteolysis.

Correspondence: Han-Mou Tsai
Montefiore Medical Center/Albert Einstein College of Medicine, Division of Hematology, Bronx, NY 10467; e-mail: htsai@montefiore.org

Table 1. ADAMTS13 levels in patients with heparin-induced thrombocytopenia

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of cases</th>
<th>Range in patients, % (normal range, %)</th>
<th>No. of cases no more than 30%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bianchi et al</td>
<td>16</td>
<td>10-100 (&lt; 50)</td>
<td>5</td>
</tr>
<tr>
<td>Tsai et al</td>
<td>18</td>
<td>48-160 (78-127)</td>
<td>0</td>
</tr>
</tbody>
</table>

References

