Hyperleukocytosis and Leukostasis: Common Features of Childhood Chronic Myelogenous Leukemia

By Jacob M. Rowe and Marshall A. Lichtman

Ten patients under 20 yr of age with the usual (adult) type of chronic myelogenous leukemia (CML) were seen at the University of Rochester Medical Center from 1970 to 1982. The mean white cell count in these 10 patients at presentation was 360,000/µl, as compared to a mean of 137,000/µl in 80 CML patients over 20 yr of age seen during the same time interval (p < 0.02). Analyses of all 90 cases revealed a significant decrease in the average leukocyte count at presentation with increasing age. The childhood cases also had a significantly higher proportion of blood blasts, promyelocytes, and myelocytes than did the adult subjects (p < 0.01). Signs of leukostasis were present in 12% of adult cases as compared to 60% of the 10 childhood cases, and in these 6 subjects, the mean white cell count was 510,000/µl. In these 6 patients, leukapheresis and/or chemical therapy was initiated rapidly, and this was followed by complete resolution of the clinical signs of leukostasis.

A review of the literature from 1960 to 1982 identified 61 childhood cases that were reported with the usual type of CML. In this group, the frequency of hyperleukocytosis and the distribution of white cell counts corresponded very closely to the 10 cases studied at the University of Rochester. Thus, the usual type of CML presenting in childhood differs from that of adults in that hyperleukocytosis, blood granulocyte immaturity, and leukostatic central nervous system, retinal, and respiratory signs are significantly more common and extreme and merit rapid cytoreductive treatment.

MATERIALS AND METHODS

Medical records of all patients at the University of Rochester who presented with leukemia between the years 1970 and 1982 were reviewed. The presenting clinical features, white cell and differential count, packed red cell volume, platelet count, marrow morphology, chromosome analysis, hemoglobin electrophoresis, and leukocyte alkaline phosphatase scores were noted. The leukocytosis (milliliters packed leukocytes/deciliter blood) was calculated from the product of the white blood cell count and mean leukocyte volume of CML cells (average of 425 cu µm). The total cytocrit was obtained from the sum of the hematocrit (milliliters packed red cell count/deciliter blood) and the leukocytosis. The calculated viscosity was determined from a nomogram, which predicts the blood viscosity from the erythrocytosis and leukocytosis. The diagnosis of leukostasis was made based on the presence of respiratory, central nervous system, and retinal abnormalities in the absence of other etiologic factors. All patients with central nervous system signs had negative CAT scans and a normal cytologic analysis of a cytocentrifuged sample of spinal fluid. The initial therapy and the response to therapy prior to the initiation of chronic phase treatment were recorded.

The cases of children with the usual type of CML who were reported in the literature from 1960 to 1980 were reviewed. In 61 subjects, the presenting white cell and platelet counts were available, and the presenting packed red cell volume was available in 55 of these 61 cases. The only reports included in this review were those in which blood cell counts for individual patients at the time of presentation were included. These subjects were compared with the cases of CML in children and adults from the University of Rochester.

Statistical analyses were performed using the independent samples t test for comparison of the blood counts in the various groups. Linear or curvilinear regression analyses were performed to determine the relationship between the percent of blood granulocyte precursors and the total leukocyte count, the hematocytosis and leukocytosis, and the presenting white cell count and the age of the patient.

RESULTS

Characteristics of Childhood Cases

Ten patients ranging in age from 2 to 19 yr, with a mean age of 12.6 yr, presented with the usual type of CML (Table 1). This represented 5.5% of all child-
Table 1. Cases of Childhood Chronic Myelogenous Leukemia at the University of Rochester Medical Center, 1970–1980

<table>
<thead>
<tr>
<th>ID</th>
<th>Age</th>
<th>Sex</th>
<th>Initial Therapy</th>
<th>Survival</th>
<th>Ph</th>
<th>Cytogenetic Evidence of Chromosome</th>
<th>Signs of Leukostasis</th>
<th>Signs of Leukemia</th>
<th>Total Cytocrit</th>
<th>Cytocrit</th>
<th>Packed Cell Volume (ml/dl)</th>
<th>Packed Cell Volume (No./μl)</th>
<th>Packed Cell Volume (ml/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>488 F</td>
<td>15</td>
<td>786,000</td>
<td>5</td>
<td>None</td>
<td>Yes</td>
<td>Left pellipapule, bilateral splenomegaly</td>
<td>+ + +</td>
<td>Leukapheresis</td>
<td>75</td>
<td>Cytosan</td>
<td>67,000</td>
<td>54</td>
<td>15</td>
</tr>
<tr>
<td>395 F</td>
<td>10</td>
<td>610,000</td>
<td>40</td>
<td>None</td>
<td>Yes</td>
<td>Bilateral fundal changes, tinnitus</td>
<td>+ + +</td>
<td>Leukapheresis</td>
<td>49</td>
<td>ARA-C</td>
<td>334,000</td>
<td>50</td>
<td>15</td>
</tr>
<tr>
<td>301 M</td>
<td>15</td>
<td>568,000</td>
<td>63</td>
<td>Cytoxan</td>
<td>Yes</td>
<td>Bilateral pellipapule, sensory deficit right lower leg, &quot;acute respiratory distress syndrome&quot;</td>
<td>+ + +</td>
<td>Leukapheresis</td>
<td>33</td>
<td>Myleran</td>
<td>393,000</td>
<td>61</td>
<td>15</td>
</tr>
<tr>
<td>254 M</td>
<td>11</td>
<td>546,000</td>
<td>36</td>
<td>Cytoxan</td>
<td>Yes</td>
<td>Bilateral pellipapule, bilateral clonus</td>
<td>+ + +</td>
<td>Leukapheresis</td>
<td>38</td>
<td>Myleran</td>
<td>760,000</td>
<td>53</td>
<td>11</td>
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<tr>
<td>481 F</td>
<td>8</td>
<td>314,000</td>
<td>29</td>
<td>Hydroxyurea</td>
<td>Yes</td>
<td>Bilateral pellipapule</td>
<td>+ + +</td>
<td>Leukapheresis</td>
<td>26</td>
<td>None</td>
<td>1,118,000</td>
<td>54</td>
<td>8</td>
</tr>
<tr>
<td>450 F</td>
<td>13</td>
<td>309,000</td>
<td>37</td>
<td>None</td>
<td>No</td>
<td>—</td>
<td>+ + +</td>
<td>Leukapheresis</td>
<td>14</td>
<td>None</td>
<td>500,000</td>
<td>37</td>
<td>13</td>
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<tr>
<td>496 M</td>
<td>19</td>
<td>236,000</td>
<td>41</td>
<td>Leukapheresis</td>
<td>Yes</td>
<td>Bilateral fundal changes, severe impaired mental function</td>
<td>+</td>
<td>Leukapheresis</td>
<td>41</td>
<td>Myleran</td>
<td>244,000</td>
<td>28</td>
<td>19</td>
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<tr>
<td>426 M</td>
<td>19</td>
<td>130,000</td>
<td>39</td>
<td>None</td>
<td>No</td>
<td>—</td>
<td>+ + +</td>
<td>Leukapheresis</td>
<td>43</td>
<td>None</td>
<td>77,000</td>
<td>22</td>
<td>19</td>
</tr>
<tr>
<td>279 M</td>
<td>14</td>
<td>63,000</td>
<td>23</td>
<td>None</td>
<td>No</td>
<td>—</td>
<td>+ + +</td>
<td>Leukapheresis</td>
<td>17</td>
<td>None</td>
<td>24,000</td>
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<td>14</td>
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<tr>
<td>472 M</td>
<td>2</td>
<td>40,000</td>
<td>33</td>
<td>None</td>
<td>No</td>
<td>—</td>
<td>+ + +</td>
<td>Leukapheresis</td>
<td>43</td>
<td>None</td>
<td>1,590,000</td>
<td>42</td>
<td>2</td>
</tr>
</tbody>
</table>

*Table 1. The total cytocrit is the sum of the hematocrit and the calculated leukocrit (cell count x mean cell volume). The leukocrit one would observe in a spun tube would be higher because the poorly deformable leukocytes do not pack completely. Thus, the total cytocrit in a spun tube would be higher than the value noted in this table. The leukocyte alkaline phosphatase (LAP) score was below 10 in all patients, except in patient 301 in whom it was 15 (normal 11–95). The fetal hemoglobin level (HbF) was below 3% in all patients.

Table 2. Blood Counts in Childhood and Adult CML

<table>
<thead>
<tr>
<th>Group</th>
<th>Age</th>
<th>No.</th>
<th>Mean</th>
<th>Median</th>
<th>Standard Error</th>
</tr>
</thead>
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<tr>
<td>0–19</td>
<td>10</td>
<td>360,000</td>
<td>311,000</td>
<td>80,000</td>
<td></td>
</tr>
<tr>
<td>20–39</td>
<td>11</td>
<td>194,000</td>
<td>190,000</td>
<td>28,000</td>
<td></td>
</tr>
<tr>
<td>40–59</td>
<td>24</td>
<td>227,000</td>
<td>159,000</td>
<td>41,000</td>
<td></td>
</tr>
<tr>
<td>&gt;60</td>
<td>45</td>
<td>72,000</td>
<td>51,000</td>
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<tr>
<td>&gt;60</td>
<td>45</td>
<td>72,000</td>
<td>51,000</td>
<td>12,000</td>
<td></td>
</tr>
</tbody>
</table>

A progressive decrease in the average presenting white cell counts is observed with advancing age. The higher mean value in the third group (ages 40–59) over the second group (ages 20–39) is due to two patients with counts over 650,000. This is reflected in the greater standard error and lower median presenting white cell count.
sis of the percent of blood granulocyte precursors on total leukocyte count in all 90 patients was highly significant \((r = 0.92, p < 0.001)\) (data not shown). Thus, the percent of precursors in the blood was closely associated with total white cell count, with the former increasing as the latter increased. Hyperleukocytic patients, therefore, had the highest percentage of immature cells in the blood.

Figure 1 compares the cumulative percent frequencies of the total leukocyte count at presentation in adult CML patients, childhood CML patients at the University of Rochester, and the childhood cases from the literature review. A striking similarity in distribution was present when the childhood cases were compared, and their distribution curves were significantly different from that of adults.

The mean packed red cell volume at presentation in children was 25 ml/dl, which was significantly less \((p < 0.01)\) than the level of 32 ml/dl in 80 adult patients. The mean packed red cell volume in the 55 cases of childhood CML reported in the literature was 26 ml/dl, which is very similar to the children in our series.

An inverse relationship of hematocrit with the leukocrit was present in the 90 patients with CML seen at the University of Rochester during the period 1970–1982. For all values, this relationship is best described by a quadratic regression analysis \((r = 0.54, p < 0.01)\) (data not shown), but for white cell counts over 100,000/µl, the predicted relationship is almost linear, with a fall in hematocrit of approximately 1.0 ml/dl for each increment in leukocrit of 1.0 ml/dl.

The mean platelet count at presentation in the 10 childhood cases was 501,000/µl and was 485,000/µl in the 61 cases from the literature. Although these mean counts were higher than that in the 80 adult patients, in whom the mean platelet count at presentation was 435,000/µl, the difference was not significant (Table 2).

**Leukostasis**

Six of the ten childhood patients presented with leukostatic signs and symptoms. This compared with only 10 of the 80 adult CML patients who presented with leukostasis (Table 5). All six children had signs and symptoms affecting the central nervous system or retina, and one of the patients also had pulmonary involvement (Table 1). In all these patients, therapy was instituted quickly (leukapheresis and/or chemotherapy) and was directed at lowering the white cell count as rapidly as possible. There were no early deaths and no significant complications from this treatment. The signs and symptoms resolved in all cases as the leukocyte count was decreased. No specific central nervous system therapy was given.

**Survival**

The mean survival of all children with CML in our series was 38 mo and was 44 mo in 5 of the 6 children with the signs of leukostasis. One child is well at 38 mo (Table 1).

**Table 5. Leukostasis and Extreme Hyperleukocytosis in Childhood and Adult CML**

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>Percent of Patients With WBC &gt;250,000/µl</th>
<th>Percent of Patients With Leukostasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood CML</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(U. of Rochester)</td>
<td>10</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Childhood CML (literature)</td>
<td>61</td>
<td>58</td>
<td>Not reported</td>
</tr>
<tr>
<td>Adult CML</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(U. of Rochester)</td>
<td>80</td>
<td>15</td>
<td>12.5</td>
</tr>
</tbody>
</table>
Blood Viscosity

Only two of the six patients with leukostasis had an increased calculated bulk viscosity of blood. The other four patients with leukostasis had true cytocrines of less than 42 ml/dl, and their calculated cytocrines were similar in value to those childhood patients without leukostasis.

DISCUSSION

The hyperleukocytosis observed in this study population was similar to that in the 61 childhood cases analyzed from reports since 1960, when the Philadelphia chromosome was first described.33 The frequency of extreme hyperleukocytosis observed in childhood CML is in sharp contrast with that observed in the adult population. In fact, a progressive decrease in the average presenting white blood cell counts seems to occur with aging. There is a wide variation in presenting leukocyte count at any age, as would be expected with a disease like CML; however, there is a highly significant mean regression of white cell counts on age, leading to a marked difference in the frequency of hyperleukocytosis with age. Several authors have reported on the clinical and laboratory features of patients with CML, and these have been recently reviewed.34 Most series include all patients with CML and are not subdivided by age. The results for our 80 adult patients cannot be compared quantitatively with reports in the literature, because few studies indicate the white cell count stratified by age and no studies provide the former information and stipulate from what stage in the disease the blood cell counts were used. We have used only the initial blood cell count, which is not necessarily the highest blood cell count before therapy. The features of our patients were very similar, however, to most published series of CML.

The division of childhood and adult leukemias by age is arbitrary. In this study, subjects under 20 yr of age were considered childhood cases. One large study of children under 16 yr of age with the usual type of CML has been reported.39 If this age was used in our study, the extremes of hyperleukocytosis and anemia would have been even more pronounced (mean values of 405,000/µl and 22 ml/dl, respectively), and the incidence of the leukostasis syndrome would have been higher. The incidence of hyperleukocytosis and leukostasis would be greater also if the patient with Ph-negative CML was not included.

The direct relationship between the percentage of immature cells and the leukocyte count at the time of diagnosis of CML was even more striking than in previous reports.15,36 This highly linked relationship accounts for the increased proportion of blasts, pro-myelocytes, and myelocytes observed in cases under 20 yr of age with higher blood total leukocyte counts.

A comparison of age groups in a retrospective analysis should be interpreted cautiously because of possible unknown effects that may have been present at different times. Such factors could have acted in either older or younger patients selectively. The 20-yr span of the reports of childhood cases from the worldwide literature mitigates against this possibility, as children had higher counts than adults throughout this period. The lower presenting leukocyte counts in older patients could represent a true difference from younger patients in the expression of CML or, alternatively, the age difference could result from an earlier contact with physicians by elderly patients as a result of more frequent medical surveillance.

Signs and symptoms due to leukostasis have been reported in the hyperleukocytic leukemias and occur most frequently in CML.11 The central nervous system, the retina, and the respiratory system are most often affected, although other organ systems may be involved occasionally. Reports of leukostatic signs and symptoms are very rare in childhood CML. There are case reports of priapism in childhood CML,10,14,16,24,37 and 3 of 39 patients in one series had papilledema at presentation.10 Papilledema or other changes, such as hearing loss or deep ecchymoses, that may be related to leukostasis have been mentioned in reports without this pathophysiologic etiology being considered in the diagnosis.23,38 Some patients in the literature reported to have central nervous system leukemia may have had leukostasis. In one patient, an 8-yr-old child who presented with a total leukocyte count of 800,000/µl and papilledema but with normal spinal fluid analysis, the deafness and loss of vestibular function remained permanently.23 This child received intrathecal chemotherapy on the presumption that occult central nervous system involvement was present.

In the six children studied at the University of Rochester with signs and symptoms of leukostasis at presentation, other common causes for the central nervous system or respiratory involvement were carefully excluded. Moreover, all these patients responded completely when the leukocyte count was lowered with leukapheresis and/or chemotherapy. No specific central nervous system therapy (cranial irradiation or intrathecal chemotherapy) was instituted in any of the patients. There was no evidence to suggest that this more aggressive presentation has any prognostic significance once the initial white cell count is lowered.

The pathophysiology of the signs and symptoms of the hyperleukocytic syndrome is probably multifactorial, being related to impaired blood flow in the microcirculation, competition for oxygen in the microcircu-
lation, and possibly, invasion of vessel walls. In most cases of hyperleukocytosis, the bulk viscosity of blood is not elevated. The reason for this is twofold. First, it requires a leukocrit of over 10%–15% for a leukocyte suspension to be significantly more viscous than an equivalent volume of red cells in suspension. Second, a decrease in the packed red cell volume of an equivalent or greater extent accompanies the increase in leukocyte packed cell volume. This relationship has been previously described in smaller series of patients and the present data confirm this general relationship.

Thus, children with CML differ from adults in that hyperleukocytosis, percent of granulocyte immaturity, and leukostatic central nervous system, retinal, and respiratory signs are more common and extreme and, when present in either group, they merit rapid cytoreduction before chronic phase treatment is used.

REFERENCES

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