BRIEF REVIEW

Hyperleukocytic Leukemias: Rheological, Clinical, and Therapeutic Considerations

By Marshall A. Lichtman and Jacob M. Rowe

A small proportion of patients with acute or chronic leukemia has an extraordinarily high blood leukocyte count. These high counts can result in a very high fractional volume of leukocytes (leukocrit), which is also a function of the mean leukocyte volume in different types of leukemia. Despite a high fractional volume of leukocytes, bulk viscosity of blood is usually not increased because a decrement in the fractional volume of erythrocytes accompanies the increase in leukocytes. Nevertheless, the excessive numbers of leukocytes present two major problems: first, they can seriously affect flow in the circulation of the lung, brain, and less often, other organs by obstructing microchannels or by forming aggregates and white thrombi in small veins. Moreover, leukemic blasts may compete for oxygen in the microcirculation and they may be invasive, damaging vessel walls. Second, their rapid destruction in response to cytotoxic drugs causes metabolic disturbances, especially uric acid accumulation, which can lead to obstructive uropathy.

A small proportion of cases of leukemia is associated with an extraordinary concentration of leukocytes in the blood (Fig. 1). These cases present special problems to the therapist because of the effects of leukemic blast cells in the circulation of the lung, brain, and other organs, and the metabolic effects that result when massive numbers of leukemic cells in blood, marrow, and tissues are killed simultaneously by cytotoxic drugs. In some cases, leukocyte counts are so high that blood viscosity increases above normal values. In most cases, bulk viscosity of blood is not increased above normal, although viscosity can be high in the microcirculation. Other characteristics of leukemic blast cells, such as high oxygen consumption and invasiveness, may interact with a flow alteration to lead to vascular damage and organ malfunction.

CELL DEFORMABILITY AND THE VOLUME FRACTION OF CELLS AS DETERMINANTS OF VISCOSITY

The contribution of blood cells to the bulk viscosity of blood at high flow rates is a function of two factors: the deformability of individual cells and the volume fraction of blood that the cells represent. The viscosity increases logarithmically as the fractional volume of red cells (erythrocyt) increases. Leukocytes are less deformable than are red cells, thus, viscosity increases even more dramatically as the fractional volume of leukocytes (leukocrit) increases (Fig. 2). The distinction between the viscosity of red cell and white cell suspensions becomes evident when the observed leukocytocrit measured in a high-speed microcytocrit centrifuge exceeds 15 ml/dl. The observed leukocrit is greater than the true leukocrit because of the trapped plasma between the poorly deformable leukocytes. The true leukocrit can be calculated from the product of the cell packing factor (0.7) and the observed leukocrit. In the case of the red cells, the true erythrocyt and observed erythrocyt are nearly identical.

RELATIONSHIP OF WHITE CELL NUMBER TO THE FRACTIONAL VOLUME OF THE LEUKOCYTE SUSPENSION

A very high concentration of leukocytes is required to produce a true leukocrit of over 10 ml/dl. The concentration of leukocytes that results in a given true leukocrit is a function of the mean cell volume of the
Fig. 1. The cumulative percent of subjects with a given white cell count at the time of diagnosis is depicted for patients with acute myelogenous (AML), chronic myelogenous (CML), acute lymphocytic (ALL), and chronic lymphocytic (CLL) leukemia. The number of patients with each type of leukemia is shown in parentheses. The frequency of hyperleukocytosis at the time of diagnosis is most striking in patients with CML. Since cell volume is lowest in CLI (about half that of AMI or CML cells), the leukocrit of CLI patients would have a cumulative percent slightly to the left of AMI patients. These data represent the total leukocyte count at the time of diagnosis, not the highest leukocyte count observed during the course of the disease.

leukocyte (Fig. 3). Leukemic lymphocytes have a mean cell volume that ranges from 190 to 250 cu µm, leukemic lymphoblasts from 250 to 350 cu µm, and leukemic myeloblasts from 350 to 450 cu µm. Thus, it takes nearly twice the number of leukemic lymphocytes than leukemic myeloblasts to result in a given increase in leukocrit. This difference in cell diameter and volume explains, in part, the rarity of hyperleukocytic syndromes in chronic lymphocytic leukemia even at lymphocyte counts of over several hundred thousand cells per microliter (Table 1). Specific differences in the invasiveness of cells or other factors are also important.

THE RELATIONSHIP OF ERYTHROCIT TO LEUKOCRIT

In the chronic leukemias, both myelogenous (CML) and lymphocytic (CLL), there is a strong inverse relationship of erythrocrit with observed leukocrit. As leukocrit rises, erythrocrit falls (Fig. 4). In CML, erythrocrit falls 1.1 ml/dl for each increment in leuko-

Fig. 2. The viscosity of suspensions of human leukocytes or erythrocytes in plasma. Cell suspensions were adjusted to specific packed cell volumes. The observed leukocrit (OBS) was not corrected for trapped plasma volume. True leukocrit (TRUE) corrected for trapped plasma was calculated from the product of the packing factor, 0.7, and the observed leukocrit. Leukemic lymphocytes, or myeloblasts had similar viscosities at the same packed cell volume. Viscosity was measured in a cone-in-plate viscometer at different rates of shear. The minimum apparent viscosity represents a summary value derived from the square of the slope of the regression line of the square root of shear stress on the square root of shear rate, between shear rates of 2 and 200 sec⁻¹.

Fig. 3. The packed leukocyte volume (leukocrit) in blood is plotted on the ordinate as a function of the blood leukocyte concentration on the abscissa. The relationship of leukocrit to leukocyte count is a function of the mean volume of the leukocyte type. Thus, leukocrit can be determined from leukocyte count only if one knows the mean volume of the leukocyte population. Isovolumic diagonals are shown in the figure. A leukocyte count of 500,000/µl of blood in a patient with CLL with a mean cell volume of 200 cu µm results in a true leukocrit of 10 ml/dl, whereas the same white count in a patient with CML with a mean cell volume of 400 cu µm produces a true leukocrit of 20 ml/dl. The true leukocrit can be converted to observed leukocrit by dividing by 0.7.
HYPERLEUKOCYTIC LEUKEMIAS

Table 1. Frequency of the Hyperleukocytic Syndrome by Type of Leukemia

<table>
<thead>
<tr>
<th>Type</th>
<th>No.</th>
<th>Probable Cases</th>
<th>Possible Cases</th>
<th>Total Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML</td>
<td>179</td>
<td>3 (2%)</td>
<td>6 (3%)</td>
<td>9 (5%)</td>
</tr>
<tr>
<td>CML</td>
<td>85</td>
<td>12 (14%)</td>
<td>1 (1%)</td>
<td>13 (15%)</td>
</tr>
<tr>
<td>ALL</td>
<td>143</td>
<td>4 (3%)</td>
<td>2 (1%)</td>
<td>6 (4%)</td>
</tr>
<tr>
<td>CLL</td>
<td>89</td>
<td>0</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

Data represent cases seen at the University of Rochester Medical Center from 1970 to 1981. Nine patients with CML were under 20 yr of age. Eight had the Ph' chromosome in their cells. Five of the 8 patients had white cell counts over 300,000/μl and had signs of the hyperleukocytic syndrome. Thus, about 10% of adults with CML had signs of the hyperleukocytic syndrome, whereas over 50% of children with CML had such signs.

crit of 1.0 ml/dl, and in CLL erythrocrit falls 1.5 ml/dl for each 1.0 ml rise in leukocrit. Since white cells influence bulk viscosity of blood in about the same manner as red cells until the observed leukocrit exceeds 15 ml/dl, and the fall in erythrocrit usually exceeds the rise in leukocrit, a rise in bulk viscosity of blood is very rare in hyperleukocytic leukemias and is confined virtually to cases of CML (Fig. 5). Figure 6 provides an estimate of the minimum apparent viscosity of blood at a given erythrocrit and observed leukocrit. In moderately anemic subjects, observed leukocrits over 20%–25% must be present to result in an objective increase in bulk viscosity of blood. Transfusion of large quantities of red cells before the leukocyte count is reduced also can result in hyperviscosity in hyperleukocytic leukemia and can be deleterious.

Fig. 5. The viscosity of 11 consecutive patients with hyperleukocytic leukemia is compared to that of normal subjects. Diamonds represent 5 patients with CML with leukocyte counts of 210,000–620,000/μl. Circles represent 3 patients with AML with leukocyte counts of 160,000–230,000/μl. Squares represent 2 patients with ALL with leukocyte counts of 350,000 and 750,000/μl. The triangle represents a patient with CLL with a white cell count of 890,000/μl. The open symbols represent the patients’ blood. The closed symbols represent the patients’ blood with the white cells removed but the erythrocrit unchanged. Two of 11 hyperleukocytic patients had an elevated blood viscosity, and both were patients with CML. Although viscosity of blood in the remaining 9 hyperleukocytic patients was not increased above that of healthy subjects, it was about twice that expected for the erythrocrit (closed symbols).

Fig. 4. The relationship of packed red cell volume (erythrocrit) to the packed leukocyte volume (leukocrit) in 80 patients with chronic myelogenous or lymphocytic leukemia. A close inverse correlation was present between erythrocrit and observed leukocrit (r = −0.8, p < 0.01). The sum of observed leukocrit and erythrocrit exceeded 50 ml/dl in only two patients. Such reciprocality was not seen in acute leukemia in which erythrocrit was low regardless of leukocrit, although the total packed cell volume was usually lower than that observed in chronic leukemia because of the more profound anemia when leukocrit was elevated.

EFFECTS OF LEUKOCYTES IN THE CIRCULATION: PATHOGENESIS OF THE HYPERLEUKOCYTIC SYNDROME

Histopathologic studies indicate that aggregates of blast cells and thrombi, perhaps initiated by blast cell...
aggregates, may lead to occlusion of small veins in the lung, brain, or other sites.11,17

Viscosity of blood in the microcirculation may play a role in the development of the syndrome. Viscosity in the microcirculation is a function of the plasma viscosity and the deformability of individual cells in capillaries: leukocyte passage should transiently raise the viscosity in such small channels. Moreover, flow in microchannels will fall if the diameter of poorly deformable white cells approaches that of the channel. The flow patterns of leukemic leukocytes in the microcirculation have not been studied. What vessels leukemic cells enter, and what their effects may be, can only be surmised. In vitro studies using Micropore filters and micropipettes suggest that leukemic leukocytes have properties that could lead to occlusion of vessels if the vessel caliber is 75% or less of the leukemic cell diameter. Theoretical considerations suggest that flow should be reduced in channels that are only slightly larger than the diameter of the leukocyte.6,5 With high leukocyte counts, chronically decreased flow may decrease oxygen transport to tissues, since the probability of leukocytes entering microchannels should be increased as a function of white cell count. Moreover, leukemic blast cells have an oxygen consumption rate that could contribute to deleterious effects in the microcirculation.7 By competing with tissue cells in areas of obstructed flow, oxygen tension and supply can be further reduced. In some cases the invasiveness of the leukemic blast cells may be important. This feature of the cells can lead to injury or disruption of vascular walls.35 Rare cases of leukemia have features of the hyperleukocytic syndrome without markedly elevated leukocyte counts, suggesting that special features of leukemic cells may contribute to the syndrome also. This finding may be particularly true of leukemic monoblasts and promonocytes.

CLINICAL SIGNS OF HYPERLEUKOCYTIC LEUKEMIA

High leukemic blast cell counts in AML, CML, and ALL may be associated with pulmonary signs such as tachypnea, dyspnea, and hypoxia.13,16,23 A rapid decrease in blood oxygen, which occurs in vitro in the presence of hyperleukocytosis makes PO2 measurements difficult;1,24 however, true hypoxia has apparently been observed. Nervous system signs such as stupor, delirium, dizziness, tinnitus, ataxia, visual blurring, papilledema, retinal vein distention, retinal abnormalities, or intracranial hemorrhage have been associated with hyperleukocytosis.9,20,12,17,25,27,31 Pari-pism25 and vascular insufficiency7 have been reported. Sudden death can occur, usually as a result of intracranial hemorrhage. Thus, hyperleukocytosis should be treated promptly.11,12,17 Cytoxic drugs may precipitate symptoms or signs that mimic hyperleukocytosis, perhaps as a result of loss of deformability of drug-injured leukemic blast cells20 or because of the release of procoagulants.30

TREATMENT OF HYPERLEUKOCYTOSIS

A specific white cell count cannot be used to define hyperleukocytosis or to determine the approach to therapy. In patients with acute leukemia or with the accelerated phase of CML, leukemic blast cell counts of over 50,000/μl usually require prompt treatment to decrease the cell count. Patients with leukemia and hyperleukocytosis can be treated with leukapheresis and cytotoxic therapy.24,25,31,35 A single, efficient leukapheresis usually will decrease the white cell count by 20%–60% in a few hours. Since blast cells are not adherent to glass wool, a centrifuge technique rather than a filtration technique should be used. Leukapheresis can (1) reverse the hyperleukocytic syndrome rapidly, (2) be used immediately without having to wait for the result of allopurinol to reduce the risk of uric acid nephropathy, and (3) decrease the tumor cell mass so as to minimize the extent of cytolysis-induced hyperuricemia, hyperkalemia, and hyperphosphatemia. Chemotherapy with hydroxyurea in CML or in the accelerated phase of CML, with cytosine arabinoside and anthracycline antibiotics in AML, or with vincristine, L-asparaginase, and prednisone in ALL should be used concomitantly to further reduce the leukocyte count and enhance the efficiency of leuka-
pheresis by inhibiting proliferation and thereby influx of new cells into the circulation.

In ALL, because of the extreme risk of excessive cytolysis, lower doses of cytotoxic drugs should be used until the white cell count is decreased. Early cranial irradiation has been recommended for children who are too small to have leukapheresis or for adults with severe CNS manifestations. Exchange transfusion can also be used in small children in whom leukapheresis may be difficult.36

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