The Preleukemic Syndrome

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ABSTRACT

While the preleukemic syndrome (PLS) is not a homogeneous entity, its spectrum of clinical and laboratory findings has been sufficiently characterized to allow increasing certainty in its recognition. Approximately 25 percent of these patients can be expected to develop overt acute nonlymphocytic leukemia (ANLL) within an average of two to three years, and another 40 percent will die of non-leukemic complications usually related to their cytopenias within a similar time period. The remaining patients may be stable and survive for prolonged periods. Accumulating evidence indicates that in the PLS, a stem cell neoplastic clonal proliferation has already been established and may frequently be demonstrated by cytogenic analysis or culture of marrow hematopoietic cells.

Introduction

While there are earlier references to those unusual manifestations which may occur prior to the onset of acute leukemia, Block et al3 are credited with coining the term "preleukemia" in 1953. They described a series of 12 patients with a symptom complex which was relatively unique and was almost invariably followed by acute myeloblastic leukemia.

Taken in its very broadest sense, the term "preleukemia" might include any of those conditions which are known to have an increased propensity to develop leukemia. Conceptually, those conditions might then be organized in the following manner:19

1. Well defined hematologic conditions with a high incidence of leukemic transformation: e.g., polycythemia vera, idiopathic myelofibrosis, Fanconi's anemia and paroxysmal nocturnal hemoglobinuria;
2. Non-hematologic conditions frequently associated with leukemic transformation; e.g., Down's syndrome and congenital immunodeficiency syndromes;
3. Therapeutically induced preleukemic states; e.g., leukemia following chemotherapy for other malignancies and that found in organ transplant patients who have been immunosuppressed.
4. Those patients who are exposed to known leukemogenic agents; e.g., radiation and benzene;
5. Those patients with a variety of poorly defined hematologic abnormalities which are associated with a higher than normal incidence of...
leukemic transformation, e.g., idiopathic acquired sideroblastic anemia.

While it is recognized that any of the previously mentioned groups of patients may pass through a preleukemic phase of their illness which is indistinguishable from any other group, the preleukemic syndrome, (PLS), as defined by Linman and Bagby,10 includes only the last category where there is no evident precipitating factor. It is this last group that is the subject of this report.

That the PLS is not a homogeneous grouping is emphasized by the wide variety of terms that have been used in the literature. These terms include, but are not limited to, hematopoietic dysplasia, myelodysplasia, refractory anemia, refractory anemia with hyperplastic bone marrow or excess blasts, sideroblastic anemia, pyridoxine responsive anemia, hypersplenism and, oligoblastic and smouldering leukemia. It appears that the PLS has a greater incidence than was originally thought. Retrospectively, Saarni and Linman16 suggested that 31 percent of acute myeloblastic leukemias have a recognizable PLS; however, review of bone marrow examinations at the Mayo Clinic during a 7.5 year period showed that one suspected PLS was encountered for each new acute nonlymphocytic leukemia, (ANLL), that was seen.14

There have been many objections to use of the term “preleukemia”, principally based upon the observation that not all patients with preleukemia become overtly leukemic. Undoubtedly, this is one of the reasons for the numerous non-restrictive or inoffensive terms that have been proposed as alternatives. Many authorities insist that the term “preleukemia” should be used only retrospectively after the onset of acute leukemia has occurred. Linman and Bagby,10 who have developed a set of diagnostic criteria, prefer the designation of “preleukemic syndrome”, feeling that the clinical features of that syndrome are remarkably uniform. Furthermore, they believe that such categorization will advance basic understanding of the process, and that such a designation is readily accepted by their patients as a reasonable explanation for their ill-defined affliction. They further state that their patients understand that PLS is not necessarily an irrevocable sentence to an early death. The objection that a diagnosis of PLS might “demand” immediate aggressive cytotoxic therapy is unwarranted since even with a definite diagnosis of any malignancy, the risks of cytotoxic therapy must always be weighed against the best interests of the individual patient. Certainly then, specific aggressive cytotoxic therapy should be considered only when the manifestations of the PLS pose a greater threat to the patient than the risks of the prospective treatment.

Clinical and Laboratory Features of the Preleukemic Syndrome

The preleukemic syndrome occurs in middle aged or elderly persons, that is, at an age later than the incidence ANLL without a recognizable preleukemic syndrome. While it has been observed in a few children,2 the median age approximates 60 years.10,18,16 There is a marked male predominance in most series. Approximately half of the patients are asymptomatic at the time of detection. Many initial symptoms, if present, lack specificity, although the most common symptoms are related to anemia, while bleeding or infection is found in a few patients. Physical findings also tend to be minimal and lack specificity. Lymphadenopathy is rarely present while splenomegaly is present in less than 20 percent of patients.

Hematologic abnormalities tend to be fairly uniform; in the peripheral blood, cytopenias, alone or in combination, dominate the clinical picture. Anemia tends to be constant with nonspecific anisopoikilocytosis and prominent macro-
ovalocytosis. A secondary population of hypochromic cells is sometimes present.

Circulating megaloblastoid, nucleated, red blood cells are found in two-thirds of the cases, and slight reticulocytosis is present in approximately half of the patients. The majority of the patients are leukopenic, while less frequently encountered findings include monocytosis and the presence of immature granulocytes, Pelger-Huet-like anomaly, and giant hypersegmented neutrophils. Thrombocytopenia is the most common quantitative change in platelets while large and/or abnormally granulated platelets are found in virtually all cases.

The marrow is always abnormal and usually hyperplastic with erythroid and megakaryocytic abnormalities dominating the picture. Erythroid precursors are increased and megaloblastoid, while stainable marrow iron is increased; sometimes ringed sideroblasts are prominent. Despite the usual peripheral thrombocytopenia, megakaryocytes are usually increased in number and of abnormal morphology. In most cases the granulocytic and monocytic cell lines reveal little to support the diagnosis of evolving leukemia. There may be a slight increase in cells at the myelocyte-meta-myelocyte stage, but blasts are not increased and Auer rods have not been observed.

Since much of the description resembles Vitamin B-12 and folate deficiency, it should be noted the Vitamin B-12 and folate levels are normal or increased in PLS. Leukocyte alkaline phosphatase is most often low but is variable. Red cell pyruvate kinase activity is usually low.

From retrospective studies, Linman and Bagby\(^\text{10}\) have formulated prerequisite and corroborative diagnostic criteria (table I). The prerequisite criteria include: (1) macro-ovalocytic anemia; (2) megaloblastoid erythropoiesis and/or ringed sideroblasts (3) abnormal marrow megakaryocytes and/or disorderly granulopoiesis; (4) absence of overt leukemia (<5 percent myeloblasts or rubriblasts); and (5) there is neither Vitamin B-12 nor folate deficiency nor a history of cytotoxic therapy for at least six months. While none of these features is individually specific, it is Linman and Bagby’s feeling that they collectively form a recognizable clinical syndrome.

Two large long term prospective studies of PLS have recently been published revealing remarkably similar results.\(^{14,18}\) These series which were selected by criteria similar to those of Linman and Bagby\(^\text{10}\) included a total of 435 patients. At the time of the reports, 22 percent had developed ANLL and 38 percent had died of causes usually related to their cytopenias, but without evidence of overt leukemia. There were more males than females, and the patients were largely in their seventh and eighth decades of life. Physical findings in these patients were minimal although seven percent of the patients reported by Weber et al\(^\text{18}\) had splenomegaly.

### TABLE I

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<thead>
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<th>Diagnostic Criteria for Preleukemia*</th>
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<tr>
<td><strong>A. Prerequisites</strong></td>
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<tr>
<td>1. Peripheral blood</td>
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<td>a. Anemia</td>
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<td>b. Oval macrocytosis</td>
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<tr>
<td>2. Bone marrow</td>
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<tr>
<td>a. Megaloblastoid erythropoiesis and/or ringed sideroblasts</td>
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<td>b. Abnormal megakaryocytes and/or disorderly granulopoiesis (e.g., a maturation &quot;bulge&quot; at the myelocyte stage)</td>
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<td>c. Absence of overt leukemia (&lt;5% myeloblasts or rubriblasts; no Auer bodies)</td>
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<td>3. Other</td>
</tr>
<tr>
<td>a. Absence of vitamin B-12 and folate deficiency</td>
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<tr>
<td>b. No cytotoxic therapy in past six months</td>
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<td><strong>B. Corroborative findings</strong></td>
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<tr>
<td>1. Peripheral blood</td>
</tr>
<tr>
<td>a. Nucleated red cells and/or immature granulocytes</td>
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<tr>
<td>b. Hypochromia with adequate or increased iron stores</td>
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<tr>
<td>c. Bizarre platelet size and granulation</td>
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<td>d. Thrombocytopenia</td>
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<td>e. Neutropenia</td>
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<td>f. Monocytosis or atypical monocytoid cells</td>
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<td>g. Neutrophilic hyposegmentation (i.e., Pelger-Huet-like anomaly)</td>
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<tr>
<td>2. Bone marrow</td>
</tr>
<tr>
<td>a. Erythrocytic hyperplasia</td>
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<tr>
<td>b. Megakaryocytic hyperplasia</td>
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Several other smaller studies have reported a total of 156 patients with a cumulative 47 percent leukemic transformation. Whereas Pierre’s cases excluded patients with over five percent blasts in their bone marrow, and Weber et al do not specifically address blast content, many of the smaller groups included patients with increased blasts and promyelocytes in the marrow. In fact, in the report of the Cooperative Group of 58 cases of refractory anemia with excess of blast cells, which included only cases with from 10 to 40 percent blasts plus myeloblasts and promyelocytes in their bone marrow, the highest leukemic transition, namely 60 percent, was reported. Similarly, in the report of Ricci et al. only those two patients with excess blasts, 11 and 21 percent, respectively, developed acute myeloblastic leukemia. Two others with normal blast content developed subacute myeloid leukemia.

These data support the concept that the percentage of blasts in the marrow is generally considered to be the most significant prognostic factor for leukemic transformation. On the other hand, Dreyfus, in his report of refractory anemia with an excess of myeloblasts, showed only 28 percent transformation to acute leukemia. While indicating that some authors might regard his cases as authentic leukemia, Dreyfus cites their variable clinical course and frequent failure to progress to overt progressive leukemia as evidence that they represent a variant of the PLS.

In the vast majority of instances, the reported leukemic transformation was acute myeloblastic leukemia although smaller numbers of acute myelomonocytic and erythroleukemias were included, and Ricci et al reported two cases as subacute myeloid leukemia. The leukemic transformation occurred within a mean of 36 months, after the recognition of the PLS in the report of Weber et al, and in a median time of 19.1 months in Greenberg and Mara’s series. The reports emphasized the generally short survival after blast transformation, e.g., death occurred within a median of five months in Lidbeck’s patients. In addition, it has frequently been cited that the ANLL which follows PLS tends to be more aggressive and less responsive to chemotherapy than that ANLL which develops without a recognizable antecedent PLS.

While many PLS patients survive for many years, larger numbers die of causes other than leukemic transformation. Usually their deaths are related to cytopenia, i.e., most frequently bleeding complications followed by infections. Forty percent of the patients in the series of Weber et al died of non-leukemic causes within a mean follow up time of 35 months. Pierre reported a median survival of 24 months in 37 percent of such patients and 48 percent of Lidbeck’s patients died of non-leukemic causes with a median survival of only six months. While it might be argued that large numbers of these elderly patients with PLS could be expected to die of other causes, Pierre compared his PLS patients to age and sex-matched population controls and showed a highly significant greater mortality among the PLS group. He concluded that the PLS is a serious disorder with a poor prognosis for survival even if acute leukemia does not supervene. This is further substantiated by Greenberg and Mara’s report that the 18.9 months median survival in their series was similar for both those patients who developed leukemia and those who did not. In most series, however, survivals were shorter when leukemic transformation occurred.

Clinical factors which might be predictive of a leukemic transformation or a poor prognosis have been somewhat variable. Thus, while Greenberg and Mara indicated that pancytopenia at presentation of the PLS was predictive of leukemic transformation, the larger study
of Weber et al\textsuperscript{18} drew the opposite conclusion. Lidbeck\textsuperscript{9} observed an overall malignant course in patients with bleeding tendencies, low platelet counts and with a severe myeloid maturation defect in the marrow (>30 percent myeloblasts and promyelocytes). Furthermore, increased serum Vitamin B-12 and the presence of myeloblasts, promyelocytes, and abnormal monocytoid cells in the peripheral blood suggested a leukemic termination.

**Chromosome Abnormalities**

If, as many observers suspect, PLS is really the preclinical stage of acute leukemia\textsuperscript{7,8,14}, it is reasonable to expect to find a variety of factors which are shared by the two conditions. It is postulated that PLS, like ANLL, is a clonal hematopoietic stem cell neoplasm manifested functionally by abnormal hematopoietic cell maturation and ineffective hematoipoiesis. During the course of preleukemia, it appears that precursor cell maturation becomes progressively impaired with termination in the severe maturational block characteristic of ANLL. Investigation of cytogenetic abnormalities in PLS and ANLL tend to support the concept that PLS, chronic leukemia, and acute leukemia may be fundamentally similar diseases differing primarily in the rate at which the aberrant clone is expanding. To that end it has been shown that there are nonrandom cytogenetic alterations shared by ANLL and preleukemic patients. These have been identified as monosomy for chromosome 7; trisomy for 8, 9, 21 and the long arm of 1 (1 q); deletions of 5 and 20 (5 q-, 20q-); and an isochrome derived from 17 (iso 17 q).\textsuperscript{13} In addition, Pierre\textsuperscript{14} has observed that the frequency of cytogenetic abnormalities in PLS are approximately equal to those found in the acute phase of leukemia.

Cytogenetic studies have also provided practical data regarding diagnosis, prognosis and management decisions concerning patient care. Nowell\textsuperscript{13} has reported that 30 percent of 80 suspected PLS patients had a cytogenetically aberrant hemic clone. Furthermore, while only 37 percent of patients with normal chromosomes developed ANLL, 81 percent, (25 of 31), of those with chromosomal abnormalities developed ANLL. The predictive poor prognosis of a chromosomally aberrant clone appears to be true whether the patient has a mixture of abnormal and normal metaphases or only abnormal metaphases in the marrow. According to Nowell,\textsuperscript{13} there is no evidence that involvement of specific chromosomes is of particular prognostic value, although he reports that multiple alterations involving more than two chromosomes were an unusually bad sign, with 12 of 14 such patients dead within four months (nine with leukemia). Pierre’s\textsuperscript{14} conclusions were similar in that, while 30 percent of the total 284 patients with suspected PLS were found to have cytogenetic abnormalities, 53 percent of those patients who progressed to acute leukemia had cytogenetic abnormalities. He felt that the presence of cytogenetic abnormalities aided in the recognition of patients with PLS, and while they were not specific for leukemia, such patients were at a greater risk of progression to overt leukemia. When banding techniques were used, 13 of 26 patients were shown to have chromosomal abnormalities similar to those previously described in ANLL. Pierre\textsuperscript{14} concluded that patients with cytogenetic abnormalities are more likely to develop overt ANLL, and his studies supported the postulate that the PLS is simply the preclinical state of acute leukemia.

**Culture of Marrow Cells**

Soft-gel and liquid culture of myeloid marrow cells has allowed assessment of
the clonal growth of granulocytic-mono­cytic progenitor cells (CFU-GM) under the influence of colony-stimulating activ­ity in a variety of hematologic abnormalities including PLS. Similar to those findings in acute leukemia, impaired granulocy­tic-monocytic colony formation has also been noted in the majority of patients with preleukemia. Furthermore, where sequential bone marrow cultures have been performed on patients with preleu­kemia, persistent or progressively de­creasing granulocyte-monocyte stem cell cloning efficiency has occurred prior to or concomittant with transformation to acute leukemia.

To illustrate further that in pre-leu­kemia a neoplastic clone is already es­tablished, Keoffler and Golde cultured bone marrow cells of three typical PLS patients who had a stable aneuploid chro­mosome marker. These studies showed that although maturation was delayed in liquid culture, it did proceed with time. By 21 days of culture, morphologic, cytochemical, and functional evidence of maturation was observed in about 85 percent of the cells. Sequential cytogenic analysis repeatedly demonstrated that the maturing cells almost always carried the cytogenic abnormality indicating that they were derived from the neoplastic clone. When these patients later de­veloped frank acute myelogenous leu­kemia, the leukemic cells retained the same karyotypic marker of the abnormal clone. These observations suggested that the leukemic clone was predominant at the time the clinical picture could only be identified as PLS. Thus, it supported the concept that preleukemia is a clonal hematopoietic stem cell neoplasm that may be viewed as an early phase of leukemia where the neoplastic clone is established and manifested functionally by partially effective hematopoiesis. Prec­ursor cell maturation becomes progress­ively impaired with termination in the severe maturational block characteristic of acute myelogenous leukemia. Bone marrow cultures have also provided add­itional prognostic information in that it has been observed that those patients with the most markedly diminished ini­tial CFU-GM values, (≤2 colonies per 10⁶ marrow cells), have the poorest probability of survival; namely, 19 percent at two years.

Treatment

As might be expected, there is consid­erable controversy regarding how best to manage these patients clinically. While those methods associated with minimal patient risk are easily adapted, they are frequently only symptomatic in nature or of doubtful efficacy. Thus, observation and transfusions for refractory anemia form the backbone of all clinical support. Since these patients with their macrocyt­ic anemias frequently mimic Vitamin B-12 and folic acid deficiencies, those agents are sometimes used although there is no evidence of their usefulness unless individual patients have coinci­dental deficiencies in those factors. Since long term treatment with pyridoxine has been reported to be of benefit in small numbers of patients, it is frequently tried clinically. The frequency of pyridoxine responsiveness is apparently very low, however. There is also some anecdotal evidence that androgens may be helpful in PLS; however, Linman and Bagby¹⁰ have yet to see an unequivocal response. The Cooperative Group for the Study of Aplastic and Refractory Anemias¹¹ has further reported that androgens do not improve the marrow insufficiency.

Splenectomy has also been reported to result in improved peripheral blood cell values although ordinarily there should be splenomegaly and/or evidence of hypersplenism for it to be given serious consideration. The vast majority of PLS patients derive no benefit from cortico­steroids although since some do, a ther­apeutic trial of prednisone is frequently tried. Bagby et al¹¹ have also reported
the ability to detect those patients who will respond to steroids by use of an in-vitro test. When bone marrow was cultured, enhanced granulocyte-monococyte colony and cluster formation occurred after addition of hydrocortisone to the culture media in three patients who clinically responded to steroid therapy. With but two exceptions, all non-responding patients had a negative test.

The potential use of aggressive cytotoxic chemotherapy is even more controversial and accompanied by less experience. Most reports have indicated a reluctance to use toxic chemotherapeutic agents for a syndrome which lacks specific diagnostic criteria and progresses to overt leukemia in only approximately 30 percent of the patients. However, since the bulk of accumulating evidence supports the concept that PLS is actually an early form of leukemia, it might seem logical that early initiation of specific cytotoxic therapy could be beneficial when the tumor burden is still low. Furthermore, with the exception of a few cases, the response rate of prompt cytotoxic therapy in PLS has not been determined at this point. It is clear, however, that if these patients are followed until the development of overt blastic leukemia and then treated with cytotoxic chemotherapy, the response rate is much worse than for ANLL in general. This poor response has been attributed to resistance to chemotherapeutic agents as well as the advanced age of these patients. Therefore, as the ability to recognize specific patients at risk improves and as better chemotherapeutic agents are discovered, the possibility of employing aggressive cytotoxic therapy and bone marrow transplantation in the preleukemic phase of the disease warrants further investigation.

References