Recognition of Preleukemia

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ABSTRACT

Preleukemia, which can only be diagnosed retrospectively with certainty, presents multiple findings and clinical data which contribute to a pattern recognition process. The development of cytogenetic and marrow culture studies has not only provided additional criteria for diagnosis but also better indices of prognosis. Preleukemia can be considered to be an early expression of neoplastic disease that merges into smoldering leukemia and progresses to acute leukemia. However, in the prospective evaluation of a patient, the term hemopoietic dysplasia should be used since there are no criteria to predict the outcome in an individual case.

Introduction

Preleukemia may be defined as a clinical state which precedes acute non-lymphocytic leukemia; this term was introduced in the United States by Block et al. who described cytopenia and hematological abnormalities in patients who later developed acute myelogenous leukemia. A variety of terms, such as refractory anemia, sideroblastic anemia, aplastic anemia and hyperspleenism, have been used to identify an entity which can be designated preleukemia only retrospectively, since not all patients with these changes develop the disease. Chronic granulocytic leukemia, polycythemia, erythroleukemia and myelofibrosis with myeloid metaplasia as well as other recognized forms of the myeloproliferative group of diseases are excluded from this syndrome. Congenital and childhood diseases like Fanconi’s anemia, Down’s syndrome, etc., as well as patients who have been exposed to known chemicals, toxins or radiant energy with depression or injury of the bone marrow, also should be eliminated. The increased use of the term preleukemia by physicians for patients with poorly defined hematological abnormalities has presented a problem that is somewhat analogous to that described in the Biblical parable, “Many are called, but few are chosen.” Because of the biological variability and uncertainty, the term, hemopoietic dysplasia, has been recommended as a more appropriate term to use in an individual patient being evaluated prospectively. Initially it was felt that preleukemia represented the predisposition of a patient to develop acute leukemia, but that the disorder did not represent early
leukemia as such. During the past 25 years, retrospective studies of patients with this disorder and the development of more definitive diagnostic criteria for preleukemia tend to support the concept that these are patients with hematologic abnormalities secondary to a leukemic clone in the bone marrow, but in whom the disease is not yet recognizable as acute leukemia by the usual diagnostic criteria. All cell lines of the marrow stem cell are usually involved with red cell abnormalities ordinarily representing the earliest expression of the disease process. It has been estimated that 30 percent of patients with hemopoietic dysplasia develop acute leukemia and that approximately 50 percent of acute non-lymphocytic leukemias have an initial preleukemic phase. Less than 10 percent of patients with acquired idiopathic sideroblastic anemia develop acute leukemia with an estimated 1 percent of patients with aplastic or hypoplastic anemia developing this complication which also can be seen in pure red cell aplasia.

Preleukemia or hemopoietic dysplasia tends to occur in patients older than 50 years of age. There is a history of weakness and malaise with or without infection or bleeding complications. Splenomegaly and lymphadenopathy are typically absent.

Anemia is the most constant hematological finding with pancytopenia frequently present. Oval macrocytes are usually present along with occasional nucleated red cells in the peripheral blood; some poikilocytosis may be present owing to variable ineffective erythropoiesis. Rarely the erythrocytes are hypochromic, and when this is found the bone marrow contains sideroblasts. A recent report indicates that patients with ringed sideroblasts are less likely to develop leukemia than those with sideroblasts in which there are grains of ferritin randomly distributed in the cytoplasm.

Leukopenia is frequently present with small numbers of immature and atypical granulocytes in the peripheral blood; monocytosis is found rather consistently. Auer rods are not seen and an acquired Pelger-Huet anomaly may be identified. Thrombocytopenia is frequently found with some large bizarre platelets and occasional circulating megakaryocytes.

Bone Marrow in Preleukemia

The bone marrow is usually hyperplastic, although it may be normal cellular or even hypoplastic. The erythroid cells usually show megaloblastic changes as well as immaturity and hyperplasia. Electron microscopy reveals nuclear clefts and blebs in some of the normoblasts of patients with preleukemia and leukemia as well as pathologic sideroblasts. Megakaryocytes frequently are increased in number as well as increased numbers of small and atypical forms. The granulocytes frequently show less prominent changes than the erythrocytes and megakaryocytes; in spite of the megaloblastic type of erythroid changes, usually there are no giant metamyelocytes in the marrow and also no hypersegmented neutrophils in the peripheral blood. The marrow myeloid cells may show varying amounts of dysplasia with some monocytoid atypicality of the nucleus and poorly granulated cytoplasm as well as nuclear cytoplasmic asynchrony. A slight increase in the numbers of myelocytes and metamyelocytes may be seen, but the blast cells are not increased in number, i.e., less than 5 percent. At least two of the cell lines in the bone marrow should show some of these changes or abnormalities in order to establish a diagnosis with confidence, and three cell line involvement adds greater plausibility.

Biochemical Changes

Biochemical and enzymatic changes in the preleukemia state have been iden-
However the presence of these alterations increases the probability of the patient developing leukemia and if there are multiple alterations, i.e., more than two chromosomes, this predicts early death and an even greater hazard of developing leukemia. One case has been reported with a Philadelphia chromosome for over five years in the absence of hematological disease before developing acute leukemia.

**Cell Culture**

Bone marrow cells from patients with preleukemia do not mature normally when cultured in vitro. While some patients appear to have a normal growth pattern of their marrow cells, impaired colony forming capacity is related to the rate of progression to overt leukemia and is an index of the patient's prognosis. Further studies in this area are in progress in many laboratories and, hopefully, these will provide a better perspective of the diagnostic and prognostic value of this procedure.

**Diagnostic Considerations**

In an excellent retrospective study, Linman and Saarni have found that approximately 50 percent of the cases identified as preleukemic developed leukemia in 12 months and that by two years, 75 percent were leukemic. However, it is well recognized that some cases are much more indolent in nature and may have a latent period of up to 20 years. With a preponderance of occurrence in the elderly patients, the diagnosis of some cases can not be validated since the patients die of other diseases or non-leukemic hematological disorders with hemorrhage or infection prior to the development of a recognizable neoplastic process.

The relationship of preleukemia or hemopoietic dysplasia to smoldering leukemia or oligoleukemia, i.e., patients with bone marrows containing 5 to 50 per-
cent blast cells but with an indolent or smoldering clinical course, is receiving increasing attention. The chromosomal studies and in vitro cell culture of marrow cells suggest that preleukemia may be viewed as an ineffective erythroid syndrome of "early leukemia" in which the neoplastic clone is established and manifested functionally as ineffective hematopoiesis. Utilizing known data about doubling time of granulocytes in chronic myelogenous leukemia, Baserga has speculated that a preleukemic state should be present between four and nine years before the first clinical manifestations of chronic granulocytic leukemia, which would require a total number of leukemic cells of approximately 10^11. In hyperactive acute leukemia, the latent time would be not less than 70 days; however, with a less acute process, a true preleukemic disorder should precede the overt leukemia by 18 months. These projections ignore the variability of the host response to the neoplastic cells.

Biologically, preleukemia and smoldering leukemia may be variants of the same clinical state with the "tip of the iceberg" showing a little more in the smoldering leukemia. The diagnostic dilemma in preleukemia is best expressed by Brecher who compares hemopoietic dysplasia or preleukemia to cervical dysplasia which is cancerous in some, but not in all cases. Because of the apparent relationship to smoldering leukemia and the biological variability of the preleukemic syndrome, withholding chemotherapy is sound clinical judgment even though corticoid therapy has been proposed for selected patients.

Conclusions

1. Preleukemia is a valid concept as an early expression of neoplastic disease that merges into smoldering leukemia and progresses to acute leukemia.

2. The continuing effort to tighten the criteria for the diagnosis of preleukemia and the development of cytogenetic and marrow culture studies has resulted in better indices of prognosis and suitable guidelines for the management of these patients.

3. Preleukemia is an appropriate assessment if used retrospectively, but for the prospective evaluation of a patient, the term hemopoietic dysplasia should be used since there are no criteria available to predict the outcome in an individual case.

References


