The Preleukemic Syndrome

(Hemopoietic Dysplasia)

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PREFACE

Many years ago it was generally acknowledged that certain epithelial dysplasias represented precursor lesions for malignant epithelial neoplasms. Since then, a number of studies on chemical, viral, and radiation-induced carcinogenesis have documented that dysplastic "preneoplastic" lesions can be early events in the pathophysiology of neoplasia. More than 30 years ago, observant clinical hematologists and pathologists began to notice that some patients with acute leukemia had hematologic abnormalities which antedated the diagnosis of leukemia by years. A number of retrospective reviews 10 years later, the most notable of which was the careful review by Saarni and Linman, reported certain consistent morphological and clinical features of this "preleukemic phase". Not surprisingly, dysplasia of at least two hemopoietic lineages was universally found.

Together with Dr. James Linman, who at that time was with us here in Oregon, we began in 1974, a prospective sutdy of the preleukemic syndrome using criteria we derived from Linman's work. Many of our findings are reviewed here. This book has been written largely for clinicians, pathologists, and students of leukemia, cytogenetics, and hemopoiesis. In it we present historical background, define the term preleukemia, and provide for the reader a review of the essential morphological features of the syndrome. We have reviewed sideroblastic anemias, drug induced preleukemia, pure red cell aplasia, and paroxysmal nocturnal hemoglobinuria; we have attempted, where appropriate, to indicate linkage between some of these disorders and the preleukemic syndrome. We have presented a review of an interesting animal model of preleukemia, and have reviewed the cytogenetic abnormalities that characterize the preleukemic syndrome and the leukemia which follows on its heels. There are a number of chapters that review findings of studies on hematopoiesis in vitro, and finally, a chapter that reviews approaches to therapy.

While each of the authors has attempted to be comprehensive in scope, our objective has been to achieve clarity. We have focused on this objective because understanding of this syndrome by practitioners has been impeded by semantic confusion among investigators. Nonetheless, the syndrome is real, and in human terms can be devastating. It is widely recognized that the very use of the term "preleukemia" has been and still is, a hotly contested issue. Some hematologists use other terms (see Chapter 1); some insist that the term "preleukemia" is completely inappropriate. If the reader grasps the *substance* of what we mean when we use the term, we will have accomplished our goal. Whether the reader decides to use our terminology or some other term ("refractory anemia" for example) is of no concern.

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1984

THE EDITOR

Dr. Grover C. Bagby, Jr. is Associate Professor of Medicine, Head of the Division of Hematology and Medical Oncology at the Oregon Health Sciences University and the Section of Hematology and Medical Oncology at the Veterans Administration Medical Center* in Portland, Oreg. Dr. Bagby received his B.A. degree from Pomona College in Claremont, Calif. and his M.D. degree from Baylor College of Medicine in Houston, Tex. Dr. Bagby is a member of 9 professional and scientific organizations, was the recipient of 2 Career Development awards from the Veterans Administration Medical Center, and has published 35 research papers and 12 reviews and chapters. He is the Director of the Edwin E. Osgood Memorial Center for Leukemia Research at the Oregon Health Sciences University, serves on the Editorial Board of *Experimental Hematology* and on the Leukocyte Physiology Subcommittee of the American Society of Hematology. His current investigative activities involve studies on the growth and differentiation of human hematopoietic cells, studies on patients with leukemia and the preleukemic syndromes, the role of mononuclear phagocytes in regulating the humoral activity of the hematopoietic inductive microenvironment, and regulation of oncogene expression in hematopoietic cells.

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Introduction

Chapter 1

DEFINITION OF THE PRELEUKEMIC SYNDROME

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I. INTRODUCTION

Acute nonlymphocytic leukemia (ANLL) represents a group of malignant hemopoietic neoplasms diagnosed with relative ease by examining stained smears of peripheral blood and bone marrow. Patients with acute leukemia usually present with abnormal peripheral blood cell counts, especially anemia and thrombocytopenia. Stained smears and biopsies of bone marrow in such patients show marked hypercellularity and a predominance of primitive nonlymphoid blast forms, usually myeloblasts and/or monoblasts.

More than 30 years ago hematologists began to notice that some of their patients with ANLL had preexisting hematologic abnormalities and that these abnormalities antedated the leukemia by months or years.[1-3b] Retrospective studies since that time have indicated that the patients were often bicytopenic or pancytopenic and that while there was no increase in blast forms in the bone marrow,[4-7] there were obvious maturation abnormalities in the hemopoietic cell lines. Hemopoietic "lines" mean erythroid, granulocytic/monocytic, and megakaryocytic. The maturation abnormalities are often described together as "hemopoietic dysplasia". Some photomicrographic examples of hemopoietic dysplasia are presented in Chapter 2. While there was some clinical and morphological heterogeneity from case to case in retrospective series, some common themes began to emerge and were felt, at least by some, to be sufficiently characteristic to use in the development of criteria for testing in prospective studies. The results of such studies will be reviewed below and in more detail and in subsequent chapters. They have supported the notion that there exists a clinically recognizable syndrome which sometimes precedes the development of classical ANLL. This disorder is called preleukemic syndrome (PLS). While criteria (outlined in Table 1) will surely evolve with time, they are currently accepted by a number of workers involved in studies on this syndrome. In this chapter, the results of some of the original retrospective studies, from which these diagnostic criteria emerged, will be reviewed, as well as some results of more recent prospective studies, and overviews of some important studies on hematopoiesis and cytogenetics in these disorders will be presented. Because these issues will be covered in more detail in subsequent chapters this review will be brief. It has been written with the objective of developing for the reader a workable classification scheme and a broad perspective for the chapters to follow.

II. RETROSPECTIVE STUDIES

A. Early Case Reports

The first reports in the medical literature dealing with clinical syndromes preceding acute leukemia appeared in the 1940s.[1-3,9,10] The use of the term preleukemia, while commonly ascribed to Block et al.,[3] was first used by Hamilton-Paterson.[1] There followed in the next 25 years sporadic reports of what may have represented the PLS.[4,5,11,12] Saarni and Linman[4,5] estimated these cases to be 143 in number.

B. The Saarni and Linman Review

While a number of retrospective studies have now been carried out, they largely recapitulate the study of Saarni and Linman,[4,5] which remains the paradigm retrospective review of the PLS. Saarni and Linman obtained, in more than half (52%) of their patients with ANLL, a history of a preexisting but ill-defined hematological condition. Blood smears and bone marrow specimens were available for review in 26% of the 132 cases and were found to be universally abnormal.

Most (68%) of the 34 patients were men over 50 years of age. The symptoms and physical findings were not specific and merely reflected anemia (weakness, pallor), thrombocytopenia (hemostatic defects), or neutropenia (recrudescent infections). Fewer than 20% had palpable

Table 1
THE PRELEUKEMIC SYNDROME. DIAGNOSTIC CRITERIA

A. Major criteria (all of the following criteria should be met)
   1. Peripheral blood
      a. Anemia
      b. Oval macrocytes in stained blood smears
   2. Marrow
      a. Megaloblastoid erythropoiesis and or ringed sideroblasts
      b. Abnormal megakaryocytes (predominance of forms with only one or two endonuclear segments) or abnormal, disorderly granulopoiesis (a "bulge" at the myelocyte stage)
      c. Absence of overt leukemia (<5% myeloblasts, no Auer rods)
   3. Other
      a. Absence of vitamin B_{12} and folate deficiency
      b. No cytotoxic chemotherapy in past 6 months

B. Minor criteria (the following further support the diagnosis)
   1. Peripheral blood
      a. Nucleated erythrocytes and/or immature granulocytes
      b. Bizarre platelet size and granulation
      c. Thrombocytopenia
      d. Neutropenia
      e. Monocytosis
      f. Neutrophilic hyposegmentation
   2. Marrow
      a. Erythrocytic hyperplasia
      b. Megakaryocytic hyperplasia in a thrombocytopenic patient

spleens. Examination of the peripheral blood and bone marrow was more informative; 85% were anemic and almost half of the patients had pancytopenia. Other findings are shown in Table 2. Qualitative abnormalities were also reported on peripheral blood smears, most notably in the red cell series where anisopoikilocytosis, especially oval macrocytes, were noted in all patients. Other findings are outlined in Table 3. The bone marrow morphology was as consistently abnormal as the peripheral blood smears. All patients exhibited maturation defects in more than one hemopoietic lineage. Megaloblastoid erythroid maturation occurred in 88%, granulocyte maturation abnormalities (e.g., an inordinately large number of myelocytes with fewer than expected well-differentiated forms — a finding that can be described as a "maturation bulge") occurred in 85% as did atypical megakaryocyte morphology (endonuclear undersegmentation in 85%). Other marrow findings are reviewed in Table 4.

The findings of Saarni and Linman suggested that some patients with preleukemic hemopathies exhibited some remarkably consistent morphological features. Thus, although each finding by itself did not constitute a diagnostic feature (e.g., megaloblastic changes are universal in the anemias of folate or vitamin B_{12} deficiency), in the aggregate, especially in patients in whom other explanations for similar morphological finds were absent, these findings were thought to be potentially helpful and were used to create diagnostic criteria to test in prospective studies (see Table 1).

III. PROSPECTIVE STUDIES

A large number of centers have embarked upon prospective studies on patients with the PLS using criteria similar to our own.[7,13–17,36] Some of these studies are reviewed in Table 5. The diagnostic criteria varied somewhat but the incidence of leukemia in these studies was significant and ranged from 11 to 45%. Leukemia may have developed in a higher percentage of patients in studies whose diagnostic criteria were well-defined and closely resembled the Linman-Bagby criteria.[16,17] In addition 7 to 45% of these patients died during the preleukemic phase, without evolving to ANLL. These prospective studies document the

Table 2
ABNORMALITIES OF PERIPHERAL BLOOD COUNTS IN THE PRELEUKEMIC SYNDROME

	%
Anemia	85
Thrombocytopenia	68
Leukopenia	53
Pancytopenia	44

Table 3
QUALITATIVE ABNORMALITIES IN BLOOD SMEARS FROM PATIENTS WITH THE PRELEUKEMIC SYNDROME

	%
Red blood cells	
Oval macrocytes	100
Hypochromia[a]	6
Nucleated red blood cells[b]	68
White blood cells	
Promonocytes[c]	44
Neutrophilic hyposegmentation	15
Platelets	
Large bizarre[d] forms	75

[a] 20—25% in our prospective study.
[b] 20% in our prospective study.
[c] Only 25% in our prospective study.
[d] Agranular forms of platelets with giant granules.

Table 4
BONE MARROW ABNORMALITIES IN PATIENTS WITH THE PRELEUKEMIC SYNDROME

	%
Cellularity	
Increased	70
Normal	20
Decreased[a]	3
Erythopoiesis	
Megaloblastic	85
Dyserythropoiesis[b]	80
Maturation defects[c]	33
Sideroblastic	20
Granulopoiesis	
Monocytoid maturation	80
Maturation "bulge"	85
Megakaryocytes	
Increased	51
Normal	20
Decreased	30
Atypical morphology	85

[a] 10% in our prospective study.
[b] Bizarre erythroid precursors with multiple nuclei or aberrant asymmetrical nuclear shape.
[c] Primitive erythroid forms predominate.

Table 5
SOME PROSPECTIVE STUDIES ON PATIENTS WITH THE PRELEUKEMIC SYNDROME

Number of patients	Evolved to leukemia (%)	Died during Preleukemic phase (%)	Duration of preleukemia phase (months)	Refs.
22	14	45	4—48+	12
14	29	7	<12—108	30
17	24	24	3—48	31
27	11	15	15—120	32
23	30	4	7—48+	33
13	31	15	6—24+	34
43	44	23	1—223	35
33	42	12	23—84+	16
19	37	15	2—24+	17
56	45	28	4—340	13
42	40	45	5—62	36
21	33	28	1—35+	15b

applicability of these criteria in the identification of a syndrome which antedates the development of ANLL. While these criteria will certainly evolve with time as we gain some insights on a molecular level into the cell biology of this disorder, few who have carried out such studies have failed to validate the usefulness of these criteria in current medical practice.

This book is intended to be a review of the PLS as defined above. It will not deal with other syndromes known to be associated with an increased risk of acute leukemia such as the chronic myeloproliferative disorders (chronic granulocytic leukemia [CGL], polycythemia vera, agnogenic myeloid metaplasia, and essential thrombocytosis), Down's syndrome,[18-20] Fanconi's Anemia,[18,21] Bloom's syndrome,[18,22] and Kostmann's syndrome.[18,23,24] Bone marrow and peripheral blood morphology in patients with these diseases do not generally exhibit hemopoietic dysplasia. These disorders have been categorized as "secondary preleukemia" by Mayer and Canellos.[18] While this may be convenient conceptually it is important to introduce some cautionary notes for those who wish consider perpetuating this terminology. First, the evolution of acute leukemia in the patients with "secondary preleukemia" may pass through a phase of hemopoietic dysplasia ("primary preleukemia"). In fact, in our experience and in that of others[25,26] when hemopoietic dysplasia occurs, the patient with a "secondary preleukemia" is at extraordinary risk of acute leukemia. Second, one must avoid the implication that the arbitrary terms "primary" and "secondary" are of some etiologic significance. In fact, etiologically the PLS ("primary preleukemia") is acquired, and sometimes known to be secondary to exposure to mutagenic agents.[14,27] Finally, to exclude all patients with preexisting hemopoietic disorders from the "primary preleukemia" group seems arbitrary. In our institutions, we perceive the evolution to leukemia as a dynamic process. For this reason all patients meeting the criteria outlined in Table 1 are classified as having the PLS regardless of the presence of preexisiting hematologic disorders. We recognize that there is tremendous clinical and probably, etiologic heterogeneity among the disorders leading to the PLS, and exclude no one from our prospective study. Thus, for example, if a patient with polycythemia vera evolves to hemopoietic dysplasia and meets the preleukemia criteria[25,27b] we say that the patient has the PLS and a history of polycythemia vera. This approach has enabled some groups to develop data on some important prognostic features of myeloproliferative diseases.[25]

IV. THE PRELEUKEMIC SYNDROME IS AN ESTABLISHED NEOPLASM

We[14,15] and others[28,29] subscribe to the point of view that in patients with the PLS the neoplastic clone does not make its debut when overt leukemia occurs. The neoplastic clone already exists fully expanded and dominates the bone marrow in the preleukemic phase. We believe this to be true for at least four reasons. First, similar types and a similar array of cellular pathophysiological abnormalities occur in overt leukemia and the PLS. Second, both overt leukemia and the PLS are clonal hemopathies. Third, cytogenetic abnormalities occur in identical percentages of patients with ANLL and the PLS, and perhaps more importantly involve identical chromosomal rearrangements. Fourth, when evolution to leukemia occurs in preleukemia patients, cytogenetic abnormalities in the leukemic cells often remain the same as they were in the preleukemic phase. Thus, clonal evolution (at least by conventional banded cytogenetic studies) cannot account for the alteration in the behavior of the bone marrow cells in these cases.

A. Pathophysiological Abnormalities

A number of abnormalities have been described in cells from some patients with acute leukemia. Many of them, outlined in Table 6, have also been described in cells from some patients with the PLS.

B. Clonal Origin

Both overt acute leukemia and the PLS are states which are thought to derive from the growth of a single mutant hemopoietic stem cell. This widely accepted notion derives largely from cytogenetic studies using banded chromosome analyses of bone marrow cells[61,62] (reviewed below and in Chapter 9) and glucose-6-phosphate dehydrogenase (G6PD) phenotyping of leukemic and preleukemic cells in G6PD heterozygotes.[63]

C. Cytogenetic Similarities

Banded chromosome studies on marrow cells are abnormal in approximately 40% of patients with ANLL. While the changes are not as specific as they are in patients with chronic myelocytic leukemia (CML) (85 to 90% of whom exhibit the Philadelphia chromosome), the rearrangements are nonrandom[64] and include trisomy 8, monosomy 7, other rearrangements involving chromosomes 5, 17, 21, and other less common abnormalities.[61,64] The cytogenetic pattern in patients with the PLS is identical; 35 to 55% of patients have abnormalities on banded cytogenetic analysis.[62] Of more importance, the changes are nonrandom and involve the same chromosomes as are found to be represented in the ANLL group.[14,15a,65,67] These changes and their potential significance will be reviewed in Chapters 5, 9, and 10.

D. Clonal Evolution

Malignant cells are cytogenetically unstable;[66] cells that exhibit chromosome abnormalities often acquire additional ones. This process has been found to occur in vitro and in vivo in a wide variety of neoplastic disorders and, in the lexicon of the cytogeneticist, is known as "clonal evolution". The most striking example of clonal evolution in clinical practice is that which occurs in patients with CGL. Unlike ANLL, marrow cell differentiation in patients with CML is morphologically normal during the "stable phase" when 85 to 90% of patients have bone marrow cells which exhibit the Philadelphia chromosome. Later in the course of an individuals disease, the disorder becomes more aggressive and acute leukemia (blast crisis) occurs (see Figure 1, Chapter 9). Blast crisis is commonly accompanied by cytogenetic clonal evolution. That is, new chromosomal abnormalities have been acquired by the Philadelphia chromosome positive cells in 80 to 90% of patients with blast crisis. The abnormalities

Table 6
PATHOPHYSIOLOGICAL ABNORMALITIES COMMON TO LEUKEMIC AND "PRELEUKEMIC" CELLS

Abnormal hemopoietic cell differentiation in vivo[37,38]
Abnormal hemopoietic cell differentiation in vitro[34,40-43]
Myeloperoxidase deficiency[54,60a,60b]
Abnormal neutrophil granulation[7,44]
Abnormal neutrophil function in vitro[56-59]
Abnormal platelet granulation[45]
Abnormal platelet function in vitro[54,60a,60b]
Marrow cells produce increased amounts of leukemia inhibitory activity (LIA)[46,47]
CFU-GM are resistant to LIA[46,47]
Elevated muramidase level in serum and urine[48,49]
Mildly elevated levels of hemoglobin F[51]
Elevated levels of hemoglobin H[52]
Increased sensitivity to in vitro lysis[53]

are nonrandom and are usually one or more of three specific types (see Chapter 9): trisomy 8, isochromosome 17 q*, and an extra Philadelphia chromosome.[67,68] Because the cytogenetic changes can be found prior to the evolution of marrow cells to a leukemic phenotype, it has been suggested that the new cytogenetic rearrangement is causally related to the subsequent "leukemic" behavior of the cells. An alternative point of view is that clonal evolution is merely a reliable epiphenomenon. Nonetheless, 10 years ago, it was suspected that clonal evolution might occur as patients with the PLS evolved to ANLL. While an occasional example of this has been seen,[69] the majority of evolved patients have, in their leukemic cells, only those chromosome abnormalities found in their "preleukemic" cells.[29,69,70] Because the majority of metaphases are abnormal in the bone marrow cells of preleukemics who exhibit abnormalities these findings represent, at least from a cytogenetic point of view, evidence that the neoplastic (leukemic) process is established during the preleukemic phase in most of these patients (see Chapter 9).[14,15a,28,29]

E. Similar Etiologies

Probably the strongest evidence that the PLS represents an established leukemic disorder derives from studies on induced leukemia in animals and humans.

1. Induced Leukemia in Experimental Animals

Studies performed in dogs at the Argonne National Laboratory (Argonne, Ill.) have documented that ANLL occurs as a late effect of continuous whole body gamma irradiation with ^{60}Co. The majority of the dogs who develop leukemia develop a clear-cut PLS 1 to 24 months prior to death and the syndrome exhibits all of the morphological features of the PLS in humans.[71] Similar morphological findings have been made in preleukemic rats following a single exposure to dimethybenzo anthracene.[72]

2. Chemical Leukemogenesis in Humans

Chemicals are known to be associated with an increased risk of acute leukemia.[73] Benzene has been associated with the development of ANLL and in certain studies, legislation controlling the use of benzene was associated with a decline in the incidence of acute leukemia.[74] Of interest are reports that in nearly every case, where data were available, a "preleukemic" syndrome of marrow dysfunction preceded the onset of leukemia.[74,75] More recently much attention has been focused upon the association of therapy with alkylating

* Instead of having two short (p) arms and two long (q) arms, isochromosome 17q (abbreviated i17q) means that the 17th chromosome has four long arms and no short arms.