Chapter 83: Classification and Clinical Manifestations of the Clonal Myeloid Disorders

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INTRODUCTION

SUMMARY

The clonal myeloid neoplasms result from acquired driver and cooperating mutations within a multipotential marrow cell, or sometimes, perhaps, a stem cell. Translocations, inversions, duplications (e.g., trisomy, tetrasomy), and deletions of chromosomes can result in (1) the expression of fusion genes that encode oncogenic fusion proteins or (2) the overexpression or underexpression of genes that encode molecules critical to the control of cell growth, programmed cell death, cell differentiation and maturation, or other regulatory pathways. Gene sequencing has also identified relevant somatic mutations in cases without an overt cytogenetic abnormality. The different mutations may result in phenotypes that range from mild impairment of the steady-state levels of blood cells, insignificant functional impairment of cells, and a modest effect on longevity to severe cytopenias and death in days, if the disorder is untreated. The somatically mutated multipotential cell from which the clonal expansion of neoplastic hematopoietic cells derives acquires the features of a stem cell and retains the ability, with varying degrees of imperfection, to differentiate and mature into each blood cell lineage. A particular disease in this spectrum of phenotypes may have altered blood cell concentrations and cell structural and functional abnormalities, and these may range from minimal to severe, involving several blood cell lineages. The effect on any one lineage occurs in an unpredictable way, even in subjects within the same category of disease. The resulting phenotypes are, therefore, innumerable and varied. In polycythemia vera or essential thrombocythemia, differentiation and subsequent maturation of unipotential progenitor cells results in blood cells nearly normal in appearance and function, but their level in the blood is excessive. Moreover, overlapping features are common, such as thrombocytosis as a feature of polycythemia vera, essential thrombocythemia, primary myelofibrosis, and chronic myelogenous leukemia. The clonal (refractory) anemias may be accompanied by functionally insignificant or very severe neutropenia or thrombocytopenia or sometimes thrombocytosis. These findings reflect the unpredictable expression of the mutant multipotential hematopoietic cell's differentiation and maturation capabilities for which the genetic explanations are not well defined. The mutant cell of origin takes on the features of a (leukemic) stem cell, responsible for sustaining the disease process. Tight relationships between the genetic alteration and phenotype occur in only a few circumstances, and even these are imperfect, for example, t(9;22)(q34;q11)(*BCR-ABL1*; p210) with chronic myelogenous leukemia and t(15;17)(q22;q21) (*PML-RARα*) with acute promyelocytic leukemia. However, most patients can be grouped into a classic diagnostic designations listed in Table 83–1. The mutant stem cells that maintain the clone may

undergo further somatic mutations over time resulting in a more aggressive phenotype, notably acute leukemia, usually of the myeloid type. An important feature of the clonal myeloid diseases is the potentially reversible suppression of normal (polyclonal) stem cells by the clonally expanded neoplastic cells. The coexistence of normal polyclonal stem cells and their competition with the neoplastic clone forms the basis for the remission-relapse pattern seen in acute myelogenous leukemia after intensive chemotherapy and the reappearance of polyclonal, normal hematopoiesis in patients with chronic myelogenous leukemia after tyrosine kinase BCR-ABL inhibitor therapy. This reciprocal relationship between the leukemic clonal and polyclonal normal stem cells may be mediated by the effects of the mass of neoplastic cells (inhibitory cytokine elaboration) and/or to the effect of the neoplastic clone on the stem cell niche and the resulting disturbance of stromal cell support for normal stem cell function.

Table 83–1.

Neoplastic (Clonal) Myeloid Disorders

I. Minimal-deviation neoplasms (no increase in blast cells [<2%] are evident in marrow)

A. Underproduction of mature cells is prominent

1. Clonal (refractory sideroblastic or non-sideroblastic) anemia[a] (Chap. 87)
2. Clonal bi- or tricytopenia[a] (Chap. 87)
3. Paroxysmal nocturnal hemoglobinuria (Chap. 40)

B. Overproduction of mature cells is prominent

1. Polycythemia vera[b] (Chap. 84)
2. Essential thrombocythemia[b] (Chap. 85)

II. Moderate-deviation neoplasms (very small proportions of leukemic blast cells present in marrow)

A. Chronic myelogenous leukemia (Chap. 89)

1. Philadelphia (Ph) chromosome-positive, *BCR* rearrangement positive (~90%)
2. Ph chromosome-negative, *BCR* rearrangement positive (~6%)
3. Ph chromosome-negative, *BCR* rearrangement negative (~4%)

B. Primary myelofibrosis[b] (chronic megakaryocytic leukemia) (Chap. 86)

C. Chronic eosinophilic leukemia (Chaps. 62 and 89)

1. *PDGFR* rearrangement-positive
2. *FGFR1* rearrangement-positive

D. Chronic neutrophilic leukemia (Chap. 89)

1. *CSF3R*-rearrangement-positive
2. *CSF3R* and *SETBP1*-rearrangement positive
3. $JAK2^{V617F}$-rearrangement positive

E. Chronic basophilic leukemia (Chap. 89)

F. Systemic mastocytosis (chronic mast cell leukemia) (Chap. 63)

1. $KITD^{816V}$ mutation-positive (~90%)
2. $KITV^{560G}$ mutation-positive (rare)
3. *FILIPI-PDGFRα*

III. Moderately severe-deviation neoplasms (moderate concentration of leukemic blast cells present in marrow)

A. Oligoblastic myelogenous leukemia (refractory anemia with excess blasts)[a] (Chap. 87)

B. Chronic myelomonocytic leukemia (Chap. 89)

1. *PDGFR* rearrangement positive (rare)

C. Atypical myeloproliferative disease (syn. atypical chronic myelogenous leukemia)

D. Juvenile myelomonocytic leukemia (Chap. 89)

IV. Severe-deviation neoplasms (leukemic blast or early progenitor cells frequent in the marrow and blood)

A. Phenotypic variants of acute myelogenous leukemia (Chap. 88)

1. Myeloblastic (granuloblastic)
2. Myelomonocytic (granulomonoblastic)
3. Promyelocytic
4. Erythroid
5. Monocytic
6. Megakaryocytic
7. Eosinophilic[c]
8. Basophilic[d]
9. Mastocytic[e]
10. Histiocytic or dendritic[f]

B. High-frequency genotypic variants of acute myelogenous leukemia [t(8;21), Inv16 or t(16;16), t(15;17), or (11q23)][g]

C. Myeloid sarcoma

D. Acute biphenotypic (myeloid and lymphoid markers) leukemia[h]

E. Acute leukemia with lymphoid markers evolving from a prior clonal myeloid disease

[a]The World Health Organization includes these disorders under the rubric of the "Myelodysplastic Syndromes," the classification of which is discussed in Chap. 87.

[b]The World Health Organization includes these three disorders under the rubric of the "Myeloproliferative Syndromes."

[c]Acute eosinophilic leukemia is rare. Most cases are subacute or chronic and formerly were included in the category of the hypereosinophilic syndromes.

[d]Rare cases of acute basophilic leukemia are *BCR*-rearrangement-negative and are variants of acute myelogenous leukemia. Most cases have the *BCR* rearrangement and evolve from chronic myelogenous leukemia (Chaps. 63, 88, and 89).

[e]See Chap. 63.

[f]See Chap. 71.

[g]The World Health Organization has designated these subtypes as separate entities. They also have phenotypes listed under phenotypic variants.[1] For example, approximately 90 percent of cases of t(8;21) AML are of the phenotype acute myelogenous leukemia with maturation. Occasional cases are of the phenotypes acute myeloblastic leukemia (no evidence of maturation) or acute myelomonocytic leukemia. Inv(16) is usually an acute myelomonocytic leukemia but can be of other phenotypes, and t(15;17) invariably manifests itself as an acute promyelocytic leukemia.

[h]Approximately 10 percent of cases of acute myeloblastic leukemia may be biphenotypic (myeloid and lymphoid CD markers on individual cells) when studied with antimyeloid and antilymphoid monoclonal antibodies (Chap. 88).

Acronyms and Abbreviations

ABL1, Abelson murine leukemia viral oncogene homologue 1; ALL, acute lymphocytic leukemia; AML, acute myelogenous leukemia; *BCR*, breakpoint cluster gene; *CALR,* calreticulin gene; CD, cluster of differentiation; *CEPBA*, CCAAT/enhancer-binding protein *α* gene; CML, chronic myelogenous leukemia; FGFR, fibroblast growth factor receptor; FLT-3, FMS-like tyrosine kinase 3; G-banding, Giemsa banding; GPI, glycosylphosphatidylinositol; inv, inversion; JAK2, Janus kinase 2; miRNA, microribonucleic acid; *MPL*, myeloproliferative leukemia virus gene; *NPM1*, nucleophosmin 1 gene; PDGFR, platelet-derived growth factor receptor; PNH, paroxysmal nocturnal hemoglobinuria; t, translocation; WHO, World Health Organization.

A wide array of clonal (neoplastic) syndromes or diseases can result from somatic mutations in a multipotential hematopoietic progenitor cell (Table 83–1). This mutated neoplastic cell behaves like a hematopoietic stem cell (albeit, a cancer or leukemia stem cell), in that it is self-replicating, can differentiate, and feed progenitor cells into the various hematopoietic lineages. These leukemic, unipotential progenitors can undergo varying degrees of maturation to phenocopies of mature blood cells. Strong circumstantial evidence has existed for a myelogenous leukemia stem cell for approximately 60 years. This concept has been buttressed by experimental verification of such cells by transplantation of the human disease into immunodeficient mice[1] and by techniques to isolate and characterize their stem cell phenotype.[2,3] Although most attention has been given to the leukemic stem cell in acute myelogenous leukemia (AML) and chronic myelogenous leukemia (CML), it is very likely that a similar cell underlies (initiates and sustains) each of the phenotypically distinctive clonal myeloid diseases.

The clonal myeloid diseases can be grouped, somewhat arbitrarily, by their degree of malignancy, using the classic terminology of experimental carcinogenesis, which considers the degree of loss of differentiation and maturation potential and the rate of progression of the disease. Thus, myeloid malignancies can be viewed in the spectrum of minimally to severely deviated neoplasms (leukemias). The term *deviation* refers to the relationship of the disease in question to normal cellular differentiation and maturation and the regulation of cell population homeostasis (birth and death rates). This terminology has been used here to array the diagnostic categories of clonal hematopoietic diseases into a framework related to their pathogenesis for the reader. This approach is an effort to encourage thinking about these somewhat arbitrary diagnostic categories in pathobiologic terms and not just as a list of conditions or by epiphenomena such as disturbed morphology of blood cells that is shared to varying degrees in all categories of these disease (e.g., the dysmorphia of primary myelofibrosis is as dramatic as that of clonal cytopenias or oligoblastic myelogenous leukemia, so-called myelodysplastic syndromes.)

MINIMAL-DEVIATION CLONAL MYELOID DISORDERS

The neoplasms in this category in Table 83–1 retain a higher degree of differentiation and maturation capability and permit median life spans measured in decades without treatment or with minimally toxic treatment approaches.[4] Use of the term *minimal-deviation* should not be construed as indicating these conditions do not have morbidity, shorten life, and have other consequences to the patient. The term is used

relative to AML, in which differentiation and maturation and regulation of cell proliferation and cell death are profoundly disturbed, and in which expected life span is measured in days to weeks, if untreated. The minimal-deviation clonal myeloid diseases include one group in which late precursor apoptosis (ineffective myeloproliferation) is characteristic (the clonal cytopenias) and one group in which proliferation is exaggerated and cellular maturation approximates normal (effective myeloproliferation).

PRECURSOR APOPTOSIS PROMINENT

The clonal (refractory) anemias and bi- and tricytopenias are characteristic of this category. Cytopenias resulting from exaggerated apoptosis of marrow late precursors (referred to as "ineffective hematopoiesis") are a principal feature of this subgroup of clonal hematopoietic multipotential cell diseases. A common additional characteristic is variable dysmorphogenesis of blood cells. The blood cell abnormalities, characteristic of the clonal anemias, bicytopenias, or pancytopenia, include abnormalities of (1) red cell size (macrocytosis, anisocytosis), shape (poikilocytosis), and cytoplasm (basophilic stippling), (2) neutrophil nuclear or organelle structure (cytoplasmic hypogranulation, nuclear hypolobulation or hyperlobulation and condensation), and (3) platelet variation in size (megathrombocytes) and granulation (hypogranulation or abnormal granulation). These structural changes are the result of neoplasia. Abnormal maturation of blood cells may also leads to biochemical and functional alterations of the cells, such as disturbed hemostasis, despite adequate platelet numbers, and dysfunctional phagocytes. Dysmorphic changes in marrow precursors are evident, also (Chap. 87). Ineffective erythropoiesis, the intramedullary, apoptotic death of late erythroblasts before they reach full maturation and release, is a common feature, a major factor in development of anemia. Ineffective granulopoiesis and thrombopoiesis also occur, resulting in varying degrees of neutropenia and thrombocytopenia, despite a cellular marrow.

There is no clinical distinction in the presenting manifestation or the course of clonal anemia with less than 15 or equal to or greater than 15 percent pathologic sideroblasts in the marrow,[5] not surprisingly, as there is no pathobiologic basis for this arbitrary boundary. Therefore, this distinction nonsideroblastic vis-à-vis sideroblastic clonal (refractory) anemia has no nosologic or clinical utility, although the World Health Organization (WHO) has retained it.[6] Indeed, the clonal anemias frequently have some degree of pathologic sideroblasts in the marrow, and, thus, usually have some degree of sideroblastic erythropoiesis. Another important feature of these syndromes is that there is no quantitative evidence of leukemic blast cells in marrow or blood. If marrow blasts are elevated above the normal upper limit of 2 percent, the disorder should be considered oligoblastic myelogenous leukemia (synonym: *refractory anemia with excess blasts*; see "Moderately Severe-Deviation Disorders" below).

The WHO has defined "AML" as having equal to or greater than 20 percent leukemic blast cells in marrow; whereas, a marrow with fewer blasts (5 to 20 percent) is referred to as refractory anemia with excess blasts (e.g., one of the myelodysplastic syndromes). The use of an arbitrary boundary of 20 percent blasts has no pathobiologic basis.[7,8] In addition, the use of less than 5 percent of blasts as a threshold to distinguish clonal anemia (refractory anemia) from oligoblastic myelogenous leukemia (refractory anemia with excess blasts) is an anachronism that dates back approximately 60 years to a time when supportive care was inadequate for

children undergoing newly developed multidrug chemotherapy for acute lymphoblastic leukemia (ALL). At that time, the mid-1950s, there was no accessibility to platelet transfusions. There were very limited antibiotic options and no antifungal agents. There were no venous access devices. The risk of death during prolonged posttherapy marrow aplasia was substantial and it was not yet evident that intensive antileukemic therapy would produce a net benefit to the children so treated. In children with ALL, there were often occasional residual atypical lymphoid cells in the marrow after treatment. To deal with these circumstances an arbitrary threshold of less than 5 percent atypical lymphoid cells (suspected blasts) was used as a measure of successful induction therapy to avoid an unnecessarily long period of posttreatment–induced aplasia.[7] That boundary, however, was not intended to be a threshold to be used at the time of diagnosis. The normal myeloblast percentage is a very tightly regulated variable (mean: 1.0; SD: 0.4). In severe inflammatory states with leukemoid reactions, the marrow myeloblast percent is usually decreased because in this circumstance precursor cell expansion in the postblast cell myelocyte pool is greater. Three or 4 percent blast cells in the marrow at the time of presentation or suspected relapse should not be considered "normal" and is usually evidence of leukemic hematopoiesis. Indeed, in the presence of an established clonal myeloid disorder (e.g., clonal anemia), any percentage of blast cells, no matter how low the percentage is presumably part of the clone and thus "leukemic." Not surprisingly, sophisticated multicolor flow analysis has found immunophenotypic abnormalities in such blast cells indicating that they are not "normal" blasts.[9]

In no other cancer is the diagnosis defined by the proportion of cancer cells in histologic or cytologic examinations. Thus, using equal to or greater than 20 percent blasts as the basis for diagnosis of AML versus myelodysplasia represents an aberration in cancer diagnosis and has no pathophysiologic basis.[7,8] Indeed, studies have shown that there are no differences in the presenting hematologic findings or a series of prognostic genetic markers, for example, the FMS-like tyrosine kinase 3 *(FLT-3)* gene mutation in patients with 10 to 19 percent versus 20 to 30 percent marrow leukemic myeloblasts at the time of diagnosis.[7] The patient's disease features are the same regardless of whether they have 10 or 30 percent blast cells in the marrow at diagnosis; prognosis was correlated with patient age at diagnosis and the cytogenetic risk category and not the blast count. Moreover, several phenotypes of AML may have less than 20 percent blasts at diagnosis (e.g., acute promyelocytic leukemia, acute monocytic leukemia, acute myelomonocytic leukemia, and others).

The term *hematopoietic dysplasia*, later simplified to *myelodysplasia*, has become ensconced as the category into which clonal anemia, clonal multicytopenia, and oligoblastic myelogenous leukemia (refractory anemia with excess blasts) have been grouped. In strict pathologic terms, a dysplasia is a polyclonal, and thus nonmalignant, change in the cells of a tissue.[8,10] These myeloid syndromes are clonal, often have aneuploid or pseudodiploid cells in the clone, are the result of the expansion of a somatically mutated cell, and can be associated with significant morbidity and premature death; thus, they are neoplasias not dysplasias. They demonstrate clonal (genomic) instability, and each has a propensity to evolve into AML at a rate that far exceeds the incidence of the disease in the general population. The term *myelodysplasia* was proposed at a conference in Paris in 1976 at a time when prominent dysmorphogenesis and cytopenias were thought to be the singular abnormalities and arguments existed as to whether some of

these syndromes without increased blast cell percentages represented a preneoplastic (preleukemic) condition.[11] They have long been established as neoplastic (a spectrum of minimal-deviation to severe-deviation leukemias)—indeed, those with overt leukemic hematopoiesis (quantitatively increased leukemic blast cell counts), which made up approximately 50 percent of cases, were known at the time to be neoplasms—but the terminology has not been rectified.

OVERPRODUCTION OF CELLS PROMINENT

Polycythemia vera (Chap. 84) and essential thrombocythemia (Chap. 85) are clonal myeloid disorders so named because of the overaccumulation of red cells, and often neutrophils, and platelets in the blood in polycythemia, and of platelets, and to a lesser extent neutrophils, in thrombocythemia.[12] Each cell lineage is affected in each disorder, reflecting a multipotential hematopoietic cell origin, but the magnitude of the effect on each lineage differs. The decrease in red cell production in essential thrombocythemia usually is slight to mild. Polycythemia vera and essential thrombocythemia do not show morphologic evidence of leukemic hematopoiesis; the proportion of blast cells in the marrow is never increased above normal, and blast cells are never present in the blood. Hematopoietic differentiation and maturation are maintained. These are minimal-deviation neoplasms. These disorders do not have a specific cytogenetic abnormality, but approximately 95 percent of cases of polycythemia and approximately 50 percent of cases of essential thrombocythemia have an acquired mutation in the Janus kinase 2 *(JAK2)* gene. In thrombocythemia, 25 percent of patients have wild-type *JAK2* genes and mutations in the calreticulin *(CALR)* gene. A few percent of patients with thrombocythemia have nonmutated *JAK2* and *CALR* but a mutation in the myeloproliferative leukemia virus gene *(MPL;* Chaps. 84 and 85).[13,14] Several studies of comparative survival of the chronic myeloproliferative neoplasms have been reported.[4,15,16,17,18,18a] In the most comprehensive study of survival as of this writing, patients with essential thrombocythemia have only slightly decreased survival than expected over 10 years of observation, but this widens somewhat over longer periods. The difference in survival of patients with primary myelofibrosis is dramatically less than expected for age- and gender-matched unaffected persons and the survival of patients with polycythemia vera is intermediate (**Table 83–2**).[18a]

Table 83–2.

Comparative Survival Among Persons with Myeloproliferative Neoplasms

Years of Survival	Percent (%) of Cohort Alive			
	Expected	Essential Thrombocythemia	Polycythemia Vera	Primary Myelofibrosis
5	90	90	85	55
10	85	80	70	30
15	75	70	45	30
20	65	50	30	15
25	55	40	20	10

Data from Tefferi A, Guglielmelli P, Larson DR, et al: Long-term survival and blast transformation in molecularly annotated essential thrombocythemia, polycythemia vera, and myelofibrosis. *Blood* 2014 Oct 16;124(16):2507–2513.

MODERATE-DEVIATION CLONAL MYELOID DISORDERS

Primary myelofibrosis (Chap. 86) and CML (Chap. 89) classically share the features of overproduction of granulocytes and platelets and impaired production of red cells. In contrast to the minimally deviated clonal myeloid neoplasms, CML and primary myelofibrosis may have a small to moderate proportion of leukemic blast cells in marrow and blood. The most constant feature in primary myelofibrosis is the abundance of neoplastic, dysmorphic megakaryocytes and the resultant predisposition to marrow reticulin and collagen fibrosis, osteosclerosis, extramedullary fibrohematopoietic tumors, splenomegaly, and teardrop-shaped red cells (dacryocytes) in every oil immersion field on the blood film. The megakaryocytic abnormalities are so dominant and consistent in this disorder that it could be considered chronic megakaryocytic leukemia.[19] The cells in this disorder have no specific cytogenetic change, but approximately 50 percent of cases carry a mutation in the *JAK2* gene and approximately one-third have wild-type *JAK2* but a mutation in the *CALR* gene (Chap. 86).[13,14] These two mutations give primary myelofibrosis a genetic kinship with polycythemia vera and essential thrombocytosis. They are often referred to as “the myeloproliferative neoplasms,” but virtually all clonal myeloid diseases are fundamentally myeloproliferative as the term refers, principally, to marrow hematopoiesis. The clinical behavior of primary myelofibrosis is, in most cases of a progressive neoplasm with morphologic evidence, of lower-level leukemic hematopoiesis and with a median survival significantly less than polycythemia vera or essential thrombocythemia. Primary myelofibrosis is another misnomer perpetuated in the WHO classification. The fibrosis is secondary to cytokines released by

neoplastic (leukemic) megakaryocytes (an epiphenomenon) and it is the only cancer in the medical lexicon named after connective tissue fibers and not the cells in which the cancer arises.[19]

In contrast to primary myelofibrosis, CML has a rearrangement of the breakpoint cluster *(BCR)* gene on chromosome 22. The shortening of the long arm of chromosome 22 gives it the designation of the Philadelphia chromosome, now called the Ph chromosome. It can be identified by Giemsa (G)-banding cytogenetic studies in approximately 90 percent of patients with CML. This mutation is caused by and is a reflection of the translocation t(9;22)(q34;q11)(*BCR-ABL1* [Abelson murine leukemia viral oncogene homologue 1]). The *BCR-ABL1* fusion in CML cells can be found in virtually all cases studied by fluorescence *in situ* hybridization or the polymerase chain reaction. Only approximately 4 percent of patients with a phenotype indistinguishable from *BCR*-rearrangement–positive CML do not have the rearrangement (see **Table 83-1** and Chap. 89). An unrelenting increase in the white cell (granulocyte) count, anemia, splenomegaly, and a progressive course are common features of CML. Blast cells are very slightly increased in marrow and in the blood in patients with these two disorders, although this is a function of time of diagnosis in relation to the time of onset. CML, if untreated, has a very high propensity to progress through clonal evolution to acute leukemia.

Primary myelofibrosis terminates in acute leukemia in approximately 15 percent of patients. Median life span in these disorders is measured in years, but is significantly decreased compared to age- and gender-matched unaffected cohorts. Therapy is required in all cases of CML, and in most, but not all, cases of primary myelofibrosis at the time of diagnosis. Both diseases can be cured by allogeneic hematopoietic stem cell transplantation. Median life span is projected to be increased by decades in CML as a result of the introduction of tyrosine kinase inhibitors, which results in involution of the malignant clone, restoration of polyclonal normal hematopoiesis, and a reduction in the risk of transformation to an accelerated phase of the disease and to acute leukemia in many patients (Chap. 89).[20] A significant median prolongation of life (e.g., approximately median 2 years) result from JAK inhibitors in poor-prognosis primary myelofibrosis (Chap. 86).

Chronic neutrophilic leukemia, chronic eosinophilic leukemia, systemic mastocytosis, and chronic basophilic leukemia are included in this category. Chronic basophilic leukemia is a rare disease (Chap 89).[21] Chronic neutrophilic leukemia is uncommon but well described and defined (Chap. 89). Chronic neutrophilic leukemia is associated with a mutation in the colony-stimulating factor 3 receptor gene *(CSF3R)* alone (approximately 30 percent of cases), or a combination of mutated *CSF3R* and a SET binding protein gene *(SETBP1)* mutation (approximately 60 percent of cases) or the $JAK2^{V617F}$ mutation alone (approximately 10 percent of cases). Chronic eosinophilic leukemia represents cases previously called hypereosinophilic syndrome with evidence of clonal hematopoiesis involving eosinopoiesis. Some cases are associated with a rearrangement of the platelet-derived growth factor receptor-*β (PDGFR-β)* gene (these are indicted in **Table 83–1**) because they are specifically responsive to the tyrosine kinase inhibitor imatinib mesylate or to a congener (Chaps. 62 and 89). Chronic clonal eosinophilia also may be associated with a *PDGFR-α* gene rearrangement, but histopathologic examination of the marrow also may be consistent with systemic mastocytosis with eosinophilia, with sheets of spindle-shaped mast cells and intense eosinophilia in blood

and marrow. This rearrangement is usually the result of a *FIP1L1–PDGFR-α* fusion gene. Identification of this fusion gene in cases of mastocytosis with eosinophilia is important because of the sensitivity of the gene product to imatinib mesylate (or a congener). The mutation is inferred by a deletion in the *CHIC2* gene found using fluorescence *in situ* hybridization, which narrowly separates *FIP1L1* and *PDGFR-α* at chromosome 4q band 12. The cryptic deletion involving *CHIC2* is too small to be seen on standard G-banding. A clonal myeloid syndrome that includes eosinophilia and a translocation between 8p11, at the site of the tyrosine kinase domain of the fibroblast growth factor receptor-1 *(FGFR1)* gene, and several different partner chromosomes, is not responsive to imatinib mesylate. Systemic mastocytosis may have several types of *KIT* gene mutation; KIT^{V560G} is sensitive to imatinib mesylate and KIT^{D816V} is insensitive to imatinib but may be responsive to second-generation tyrosine kinase inhibitors. *PDGFR-α* mutations also may be present in the cells of patients with systemic mastocytosis and be responsive to imatinib mesylate (or a congener).[22]

MODERATELY SEVERE-DEVIATION CLONAL MYELOID DISORDERS

These disorders fall into a group that progresses less rapidly than acute leukemia and more rapidly than CML.[23,24] They have a predisposition to develop with a granulocytic and monocytic phenotype, either morphologically or cytochemically. These diseases include oligoblastic myelogenous leukemia (refractory anemia with excess blasts), chronic myelomonocytic leukemia, and juvenile myelomonocytic leukemia. Occasional patients have an atypical or unclassifiable syndrome. The “unclassifiable syndrome” designation is used for uncommon cases that do not fall into a classical or easily classifiable designation and usually are seen in patients older than age 70 years.

The subacute syndromes produce more morbidity than do the chronic syndromes, and patients have a shorter life expectancy. These are leukemic states that have low or moderate concentrations of leukemic blast cells in marrow and often blood, anemia, often thrombocytopenia, and usually prominent monocytic maturation of cells (Chap. 88). The oligoblastic myelogenous leukemias compose approximately 50 percent of the cases that have been grouped under the title *myelodysplastic syndromes.* In all other malignancies, the presence of tumor cells determines the diagnosis, such as carcinoma of the colon or the uterine cervix, whether *in situ*, invasive, or metastatic. Use of the percentage of tumor (leukemic blast) cells as a threshold for the diagnosis of leukemia versus “dysplasia” is not consistent with usual practice; hence, the preference for oligoblastic myelogenous leukemia rather than myelodysplasia for patients with a quantitative increase in blast cells (>2 percent blasts), cytopenias, and dysmorphic cell maturation.[8] Moreover, CML, chronic neutrophilic leukemia, chronic myelomonocytic leukemia, acute promyelocytic leukemia, and several other subtypes of AML invariably have fewer than 20 percent blasts in the marrow. Thus, the criteria used in the WHO classification system for clonal myeloid diseases have internal inconsistencies that can be dealt with by experts but are confusing to the less experienced and are not unifying.

A group of clonal myeloid diseases are referred to as atypical myeloproliferative disease or atypical CML (aCML) in the WHO classification. They are usually seen in older patients (>65 years), have a relatively low myeloblast percentage in marrow (<5 percent) and blood, and have an elevated white cell count ranging between 15 and 100×10^9/L, but which may be higher. They have anemia and thrombocytopenia and often

splenomegaly. The blood and marrow usually have a progressively increasing proportion of promyelocytes and myelocytes as well as neutrophils, superficially simulating the appearance of CML, hence the use of the designation “aCML.” These cases never have a rearrangement in the *BCR* gene, are not responsive to tyrosine kinase inhibitors, and have a poor prognosis with a median survival of approximately 15 to 20 months. Because the granulocytic series often has some dysmorphia (e.g., acquired Pelger-Huët nuclear anomaly), the WHO seems reluctant to call it an atypical myeloproliferative disorder, which should be done as aCML is an inadvisable term. Their inconsistency is evident in the classification of primary myelofibrosis as a myeloproliferative disorder despite florid dysmorphia of all three major lineages. Dysmorphia is a feature of most neoplastic cells, of considerable diagnostic utility, of interest cytologically, but an epiphenomenon not central to the pathobiology of the neoplasm. Atypical myeloproliferative disease (aCML) has a relatively high frequency of *CSF3R* gene mutations, akin to chronic neutrophilic leukemia. Because the mutant gene is thought to cause dysregulation evidenced by *myeloproliferation* and exaggerated neutrophil counts, it underlines the preferred terminology.

SEVERE-DEVIATION CLONAL MYELOID DISORDERS

Morphologic, histochemical, immunocytologic, and cytogenetic characteristics of cells in the blood and marrow provide the major basis for the diagnosis and classification of AML and its subtypes (Chaps. 11 and 88). Correlation among observers and between the morphologic method of classification and the monoclonal antibody reactivity-dependent classification of AML is imperfect.[25,26,27] The approach that uses morphology, immunocytochemistry, and the immunophenotype is the most inclusive because virtually all cases can be placed into a morphologic subtype. Because immunophenotyping is a standard procedure in most clinical hematopathology laboratories, the results are readily available. Classification by cytogenetics is more limited because approximately 45 percent of cases of AML do not have a discernible cytogenetic abnormality by G-banding and many cases have different infrequent abnormalities, making this approach complex. Hundreds of unique patterns of cytogenetic abnormalities have been reported in cells of patients with AML, including unbalanced structural abnormalities, such as loss of part or all of chromosome 5 or 7, numerical abnormalities, such as an additional chromosome 8 (e.g., trisomy 8), or unbalanced and balanced structural abnormalities, such as translocation between chromosomes 8 and 21 or 15 and 17, or between chromosome 11 and many chromosome partners, or any one of numerous other abnormalities involving other chromosomes.[28] Despite this heterogeneity, knowing the cytogenetic alteration is useful for estimating the probability of entering a sustained remission (risk category). For example, AML patients whose cells contain t(8;21), t(15;17), t(16;16), or inv(16) (approximately 20 percent of cases considering all age groups) are more likely to enter a prolonged remission or be cured with therapy. The cytogenetic findings may influence the drugs used for remission-induction therapy. Notably, patients with t(15;17) AML (approximately 7 percent of all new AML cases in the United States and twice that frequency in China) uniquely require use of all-*trans*-retinoic acid and arsenic trioxide to result in the best long-term outcome and, in many cases, a cure. Thus, combining light microscopy of blood and marrow with immunocytochemistry and cell-flow analysis immunophenotyping to designate the phenotypic subtype, supplemented by cytogenetics or molecular diagnostic methods, currently is the best approach to categorization of the AML subtype. The polymerase

chain reaction may be particularly useful for determining subclinical (minimal) residual disease and monitoring therapy in cases in which an appropriate genetic marker is available, such as the t(8;21) or t(15;17) (Chaps. 88 and 89).

Gene expression profiling using chips containing tens, hundreds, or thousands of relevant genes can be used to further genotype and subclassify AML into prognostic groups.[29,30] One would predict, based on cytogenetics, a large and diverse group of gene expression profiles for cases of AML. In one study of 200 cases of AML, some of 270 mutated genes among nine genes families (i.e., transcription factor, tumor-suppressor, signaling pathway, nucleophosmin encoder, DNA-methylation–related, chromatin-modifying, myeloid transcription factor, cohesion complex, and spliceosome-complex genes) were found in at least two cases.[31] Genetic analysis is currently most useful in analyzing cases with prior stratification by some relevant variable. For example, a study of patients with AML who have normal karyotypes by standard cytogenetic methods (e.g., G-banding) has identified two groups by hierarchical gene clustering with significantly different survival after current therapy.[32] Patients with AML whose cells contain a *FLT-3* internal tandem duplication also can be stratified into more discriminating prognostic groups using hierarchical gene cluster analysis.[33] Gene expression profiling can identify groups of patients with AML who have covert gene abnormalities, such as a mutation in the DNA methyltransferase gene *(DNMT3A)* or the nucleophosmin 1 *(NPM1)* gene. The former gene encodes one of a family of enzymes that catalyze the transfer of a methyl group to DNA, using *S*-adenosyl methionine as the methyl donor; and, the latter gene encodes a protein that shuttles between the nucleus and cytoplasm. Gene expression studies in AML are important because they (1) identify genes that cooperate or interact to result in a fully malignant phenotype, (2) provide potential new targets for therapy, (3) help identify patients who might benefit from early hematopoietic stem cell transplantation, (4) may be used to measure minimal residual disease,[34] and (5) may permit analysis of the mutational evolution from the earliest neoplastic cell without malignant potential to cells with additional mutations capable of developing lethal clones.[35]

Another molecular technique applied to understanding the molecular pathology of AML and to defining prognostic groups is the leukemic cell microribonucleic acid (miRNA) signature.[36,37] The miRNAs are small (19 to 25 nucleotides), noncoding RNAs that regulate messenger RNA stability and its translation into protein. miRNA signatures can be analyzed by polymerase chain reaction technology of RNA samples from leukemic cells and compared to normal or compared among different categories of AML cases. For example, miRNA analysis can distinguish among cytogenetically normal cases of AML as to their expression of different genes that influence prognosis, such as *NPM1* and the CCAAT/enhancer binding protein *α* gene (*CEPBA*). Specific microribonucleic acids (miRNAs) may regulate lineage differentiation of stem cells, indicating critical roles for these molecules in the regulation of hematopoiesis and in leukemogenesis.[38] Prognostic group stratification of AML, at the moment, has value principally in assessing the utility of using allogeneic hematopoietic stem cell transplantation as an early therapy. It also may inform the therapist about considering a clinical trial of new therapeutic combinations, if the prognostic indicators suggest use of cytarabine and an anthracycline regimen, as the backbone of therapy, is unlikely to be successful and the patient is not a candidate for allogeneic hematopoietic stem cell transplantation (Chap. 88).

TRANSITIONS AMONG CLONAL MYELOID DISEASES

Patients with minimal-, moderate-, and moderately severe-deviation clonal myeloid disorders have an increased likelihood of progressing to florid (polyblastic) AML, with a frequency ranging from approximately less than 1 percent of patients with paroxysmal nocturnal hemoglobinuria, approximately 10 percent of patients with clonal anemia, approximately 35 percent of patients with clonal bi- or tricytopenia, and as many as 66 percent of patients with oligoblastic myelogenous leukemia.[39] Approximately 30 percent of patients within the spectrum of clonal cytopenia to oligoblastic myelogenous leukemia (myelodysplastic syndromes) develop AML when the WHO boundary of equal to or greater than 20 percent blast cells is applied.[39] Approximately 15 percent of patients with polycythemia vera evolve to a syndrome indistinguishable from primary myelofibrosis and the same evolution can occur in patients with essential thrombocythemia.[40,41] Occasional cases of apparent essential thrombocythemia or rare cases of primary myelofibrosis can evolve into polycythemia vera. Apparent essential thrombocythemia with cells containing the *BCR-ABL1* fusion gene may progress to CML or acute blast crisis of CML.

Approximately 5 percent of patients with essential thrombocythemia develop AML over 20 years of observation, but this rises to 10 percent over 25 years.[18a] Approximately 12 percent of patients with polycythemia vera evolve to AML over 20 years of observation.[18a] Approximately 20 percent of patients with primary myelofibrosis progress to overt AML over 10 years of observation.[18a] Virtually all patients with CML have the potential to progress to acute leukemia of any subtype, including in about a quarter of cases to lymphoid phenotypes, although in some cases the patient enters an accelerated phase that behaves like oligoblastic leukemia before it progresses to acute leukemia. The accelerated phase of CML is associated with inadequate response to therapy, progressive anemia, bone pain, enlarging spleen, thrombocytopenia, among other changes (Chap. 89). The progression from chronic to accelerated phase or blast phase of CML, however, has been delayed in the majority of patients by the application of tyrosine kinase inhibitor therapy during the chronic phase of the disease. Determining the frequency of evolution to AML in those patients with CML who enter a complete molecular remission with tyrosine kinase inhibitors must await observations over the next decade.

This process of clonal evolution is an intrinsic feature of the genomic instability of clonal myeloid diseases. The practice of calling the result of this process “secondary AML” is obfuscating. This choice of terms is notable in the case of myelodysplastic syndrome, which is “leukemia” at the time of diagnosis. (Leukemia is defined as the neoplastic transformation of a primitive multipotential hematopoietic [myeloid] cell.) The neoplastic transformation has occurred and the progression to a more advanced myeloid neoplasm is a process quite different from the secondary AML that occurs as a result of recent chemotherapy for a lymphoma or an unrelated cancer (e.g., breast cancer). When there is progression to AML from a previously diagnosed clonal myeloid disease, it should be designated as clonally evolved AML (ceAML). This distinction is important because an effort to develop methods to prevent clonal evolution is very likely to be different from methods to prevent true secondary leukemia.

PATHOGENESIS OF CLONAL MYELOID DISEASES

In AML, a sequence of mutations in a single multipotential cell results in a clone that is severely defective and contains precursor cells that are largely unable to mature.[42,43] Proliferation of primitive progenitors is excessive when considered in absolute terms, that is, the total number of blast cells proliferating. AML is a clinical disease with many forms of morphologic expression. This variation of phenotype is consistent with the large number of genetic lesions identified and the behavior of the leukemic stem cell, which is capable of differentiation into all the blood cell lineages (**Fig. 83–1**). Hence, the asymmetrical and uncoordinated differentiation and maturation of leukemic progenitor cells may allow one or another cell type to predominate.[44] The different morphologic or cytogenetic variants of AML are each rapidly progressive, however, if not treated successfully (Chap. 88).

Figure 83–1.

Leukemic hematopoiesis in acute myelogenous leukemia. The malignant process evolves from a single mutant multipotential cell. This cell on the basis of a sequence of somatic mutations becomes a leukemia stem cell with a growth advantage in relationship to normal pluripotential stem cells. This cell originates at either level 1 or level 2 or level 3 in **Fig. 83–2**. Whether all cases of acute myelogenous leukemia originate in the pluripotential stem cell pool is still under study (see text). This cell is capable of multivariate commitment to leukemic erythroid, granulocytic, monocytic, and megakaryocytic progenitors. In most cases, granulocytic and monocytic commitment predominates, and myeloblasts and promonocytes or their immediate derivatives are the dominant cell types. Leukemic blast cells accumulate in the marrow. The leukemic blast cells may become amitotic (sterile) and undergo programmed cell death, may stop dividing for prolonged periods (blasts in G_0) but have the potential to reenter the mitotic cycle, or may divide and then undergo varying degrees of maturation. Maturation may lead to mature cells, such as red cells, segmented neutrophils, monocytes, or platelets. A severe block in maturation is characteristic of AML, whereas a high proportion of leukemic primitive multipotential cells mature into terminally differentiated cells of all lineages in patients with CML. The disturbance in differentiation and maturation in myelogenous leukemia is quantitative, thus many patterns are possible. At least five major steps in hematopoiesis are regulated: (1) stem cell self-renewal, (2) differentiation into hematopoietic cell lineages (e.g., red cells, granulocytes, monocytes, platelets), (3) proliferation (cell multiplication), (4) maturation of progenitor and precursor cells, and (5) release of mature cells into the blood. These control points are defective in acute myelogenous leukemia. Premature or delayed apoptosis of cells may be another key abnormality contributing to premature cell death or cell accumulation.

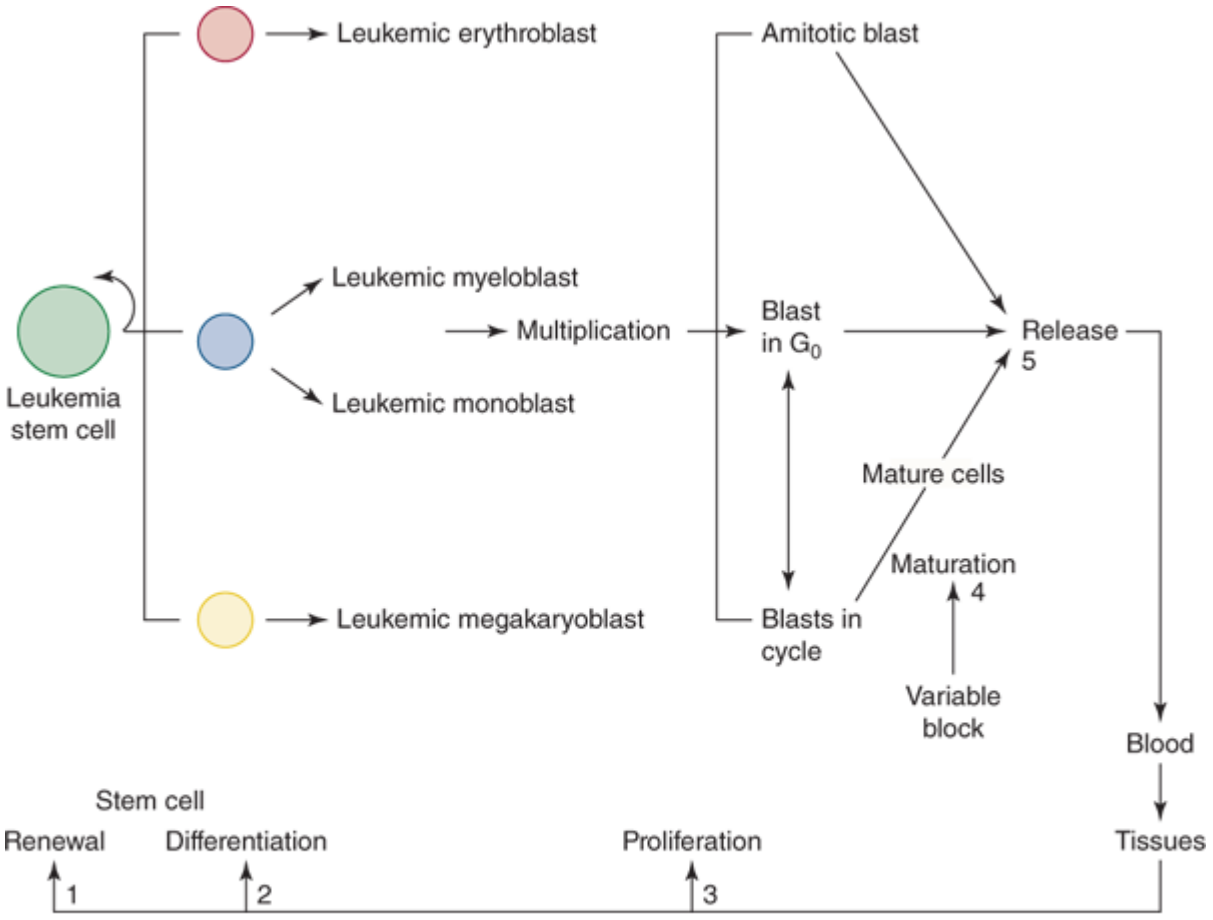
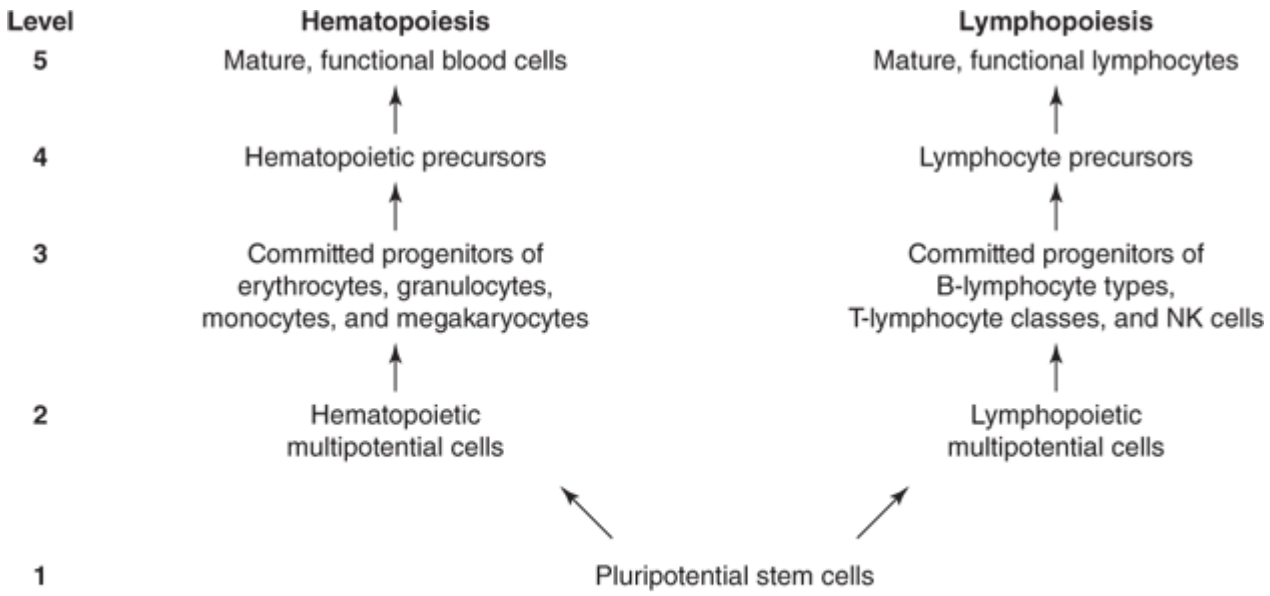


Figure 83–2.

Differentiation and maturation of hematopoietic stem cells. The functioning stem cell pool is thought to be at *level 1*, the pluripotential (lymphohematopoietic) stem cells. In healthy humans, two multipotential progenitor cell pools are operative *(level 2)*. The multipotential progenitors differentiate further to unipotential progenitors, which are sensitive to specific cytokines *(level 3)*. The committed progenitor cells are referred to as colony-forming units or colony-forming cells because they form clonal colonies of cells in semisolid medium in the presence of the appropriate growth factors. These growth factors are capable of inducing proliferation and maturation of the committed progenitor cells so that they achieve *level 4*, at which the first morphologically identifiable marrow precursors have developed, such as myeloblasts, proerythroblasts, promonocytes, megakaryocytes and, ultimately, *level 5*, the mature, functional blood cells. NK, natural killer.



Important epiphenomena are related to certain morphologic types of AML, such as tissue infiltration, including into the central nervous system in monocytic leukemia, disseminated intravascular coagulation, fibrinolysis, and hemorrhage in promyelocytic leukemia, and to a lesser extent in monocytic leukemia, hepatosplenomegaly (eosinophilic leukemia), mediator-release syndromes (basophilic or mast cell leukemia), predisposition to myeloid sarcomas (AML with t[8;21] or inv[16] cytogenetic abnormalities), and intense marrow fibrosis (megakaryocytic leukemia) (Chap. 88).

In CML, injury to a single cell results in a clone in which there is an enormous expansion of progenitors for granulocytic and, often, megakaryocytic cells. Erythropoiesis is effective but decreased. Unlike AML, maturation of progenitor cells in CML is nearly normal; hence, the predominant leukemic cells in the blood are postmitotic, mature, or partially matured cells, such as late myelocytes and segmented neutrophils, monocytes, erythrocytes, and platelets. This process of multilineage differentiation and maturation to cells with virtually normal function accounts for the relative infrequency of hemorrhage or recurrent infection in the chronic phase of CML.

Because hematopoiesis is generated by a leukemic stem cell that has functional analogies to a normal multipotential hematopoietic cell, erythropoiesis, thrombopoiesis, and granulopoiesis are leukemic in most patients with AML, CML, and other clonal myeloid diseases. Thus, identical clonal cytogenetic abnormalities are present in erythroblasts, megakaryocytes, and granulocyte precursors in cases of AML so studied (Chap. 88) and in all cases of CML with a BCR-rearrangement (Chap. 89).

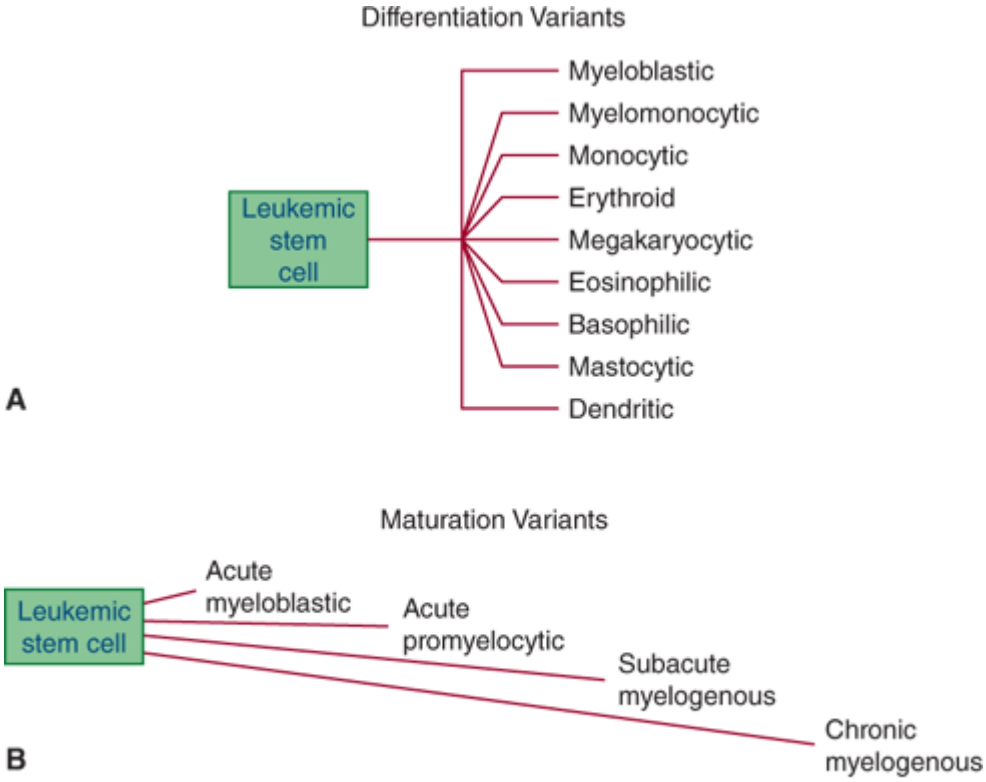
PHENOTYPE OF MYELOID CLONAL DISEASES AS A RESULT OF THE MATRIX OF DIFFERENTIATION AND MATURATION

The phenotype of clonal myeloid diseases is a reflection of a neoplastic stem cell's capability to differentiate into abnormal committed progenitor cells and the ability of those progenitor cells to mature into identifiable

cells of the erythroid, granulocytic (neutrophilic, basophilic, mastocytic, eosinophilic), monocytic, dendritic, and megakaryocytic cell lineages (Fig. 83–3).[42,45,46]

Figure 83–3.

Phenotypic subtypes of acute myelogenous leukemia. Acute myelogenous leukemia has variable morphologic expression and a variable degree of maturation of leukemic cells into recognizable precursors of each blood cell type. This phenotypic variation results because the leukemic lesion resides in a multipotential cell normally capable of all the hematopoietic lineage commitment decisions. **A.** Morphologic variants of AML can be considered differentiation variants in which the cells derived from one of the options of commitment accumulate prominently (e.g., leukemic erythroblasts, leukemic monocytes, leukemic megakaryocytes). **B.** Acute myeloblastic leukemia, promyelocytic leukemia, subacute myelogenous leukemia, and chronic myelogenous leukemia can be considered maturation variants in which blocks at different levels of maturation may be present or do not exist (e.g., CML).



Under normal circumstances, hematopoietic differentiation represents the irreversible change from a multipotential cell to multiple, unipotential lineage progenitors. Maturation represents the physical and chemical changes from a unipotential progenitor through a sequence of precursors to the fully mature and functional blood cell, including progression from a burst-forming unit–erythroid to proerythroblast to erythrocyte; from a colony-forming unit–granulocyte to myeloblast to segmented neutrophil; from a colony-forming unit–eosinophil to a segmented eosinophil; from a colony-forming unit–basophil to a mature basophil; from a colony-forming unit–mast cell to a mature mast cell; from a colony-forming unit–monocyte-macrophage to promonocyte to monocyte to macrophage or dendritic cell; and from a colony-forming unit–megakaryocyte to a diploid megakaryoblast to the polyploidy, platelet-forming megakaryocyte (Chap. 18). A

matrix, which is composed of the options of commitment to different lineages and the progressive stages of maturation at which partial or complete arrest can occur, results in the potential for a wide array of morphologic syndromes by which a leukemic stem cell can dominate hematopoiesis (see Fig. 83–2).

In the clonal myeloid diseases in which differentiation and maturation capability are retained, one of the cell lines—for example, erythrocytes, granulocytes, monocytes, or platelets—tends to accumulate in the blood more prominently and results in a phenotypic expression of the disease that determines the nosology (e.g., exaggerated blood platelet accumulation and essential thrombocythemia). In AML, the phenotypic expression may be predominantly myeloblastic (granuloblastic), erythroid, monocytic, megakaryocytic, or combinations thereof. Certain patterns are favored. In AML, myelocytic leukemia, monocytic leukemia, or a mosaic of the two cell types (myelomonocytic leukemia) are more common than erythroid or megakaryocytic leukemia. Eosinophilic, basophilic, and dendritic cell leukemias are rare. However, AML usually has a disturbance in all cell lines. In myeloblastic or myelomonocytic leukemia, overt, qualitative abnormalities of erythroblasts and megakaryocytes may occur. The prevalence of the abnormalities in the latter two lineages may not be great enough or evident enough for the observer to designate a case as erythroid or megakaryocytic leukemia. In the latter two cases, identification of markers unique for erythroid (e.g., cluster of differentiation [CD] 71) or megakaryocytic cells (e.g., CD41, CD42, or CD61), rather than reliance solely on light microscopy, has increased the frequency of identification of these variants.

The continuum of maturation can be completely or partially blocked at various levels, leading to morphologic variants such as acute myeloblastic, acute promyelocytic, AML with maturation, and CML.

PLURIPOTENTIAL STEM CELL POOL AS SITE OF THE NEOPLASTIC EVENTS

Evidence points to a lesion in the multipotential hematopoietic cell pool in most of the clonal myeloid diseases, explaining the involvement of erythropoiesis, granulopoiesis, monopoiesis, and thrombopoiesis. Debate continues whether the cell of origin is a pluripotential (lymphohematopoietic) stem cell or a somewhat more differentiated multipotential cell.[47,48] (Chapter 88 provides a more detailed discussion of this topic.) In CML patients, the mutation is thought to be in the pluripotential stem cell; in other syndromes, evidence for involvement of B, T, and natural killer (NK) lymphocytes is variable. B lymphocytes are derived from the clone in some cases. Evidence that affected T lymphocytes undergo apoptosis before entering the blood in patients with CML may explain the absence of clonal markers in T lymphocytes in some cases of CML and other clonal myeloid disorders.[49]

PROGENITOR CELL LEUKEMIA

Analysis of cases of AML in informative girls (young women) and older women who were heterozygous for X chromosome-linked gene products isotypes A and B of the enzyme glucose-6-phosphate dehydrogenase indicated that the AML clone in the young women was restricted to the granulocyte–monocyte pathway, whereas monoclonality was expressed in all hematopoietic cell lines in the older women. This approach had

been validated in prior studies of CML and AML, using enzymes or chromosome markers.[50,51] These findings supported the possibility that a leukemic transformation in young patients can occur in progenitor cells (e.g., colony-forming unit—granulocyte-monocyte; level 3 in **Fig. 83–2**) and result in a true acute "granulocytic" leukemia. If progenitor cell myelogenous leukemia is common in younger patients, this pattern might explain their better response to treatment. In a subset of patients with acute monocytic leukemia,[52] t(8;21) AML,[53] and t(15;17) AML,[54] studies indicated that the leukemia derives from the neoplastic transformation of a more differentiated progenitor cell not the pluripotential lymphohematopoietic stem cell. The acute transformation of CML also appears to occur in a granulocyte-monocyte progenitor (Chap. 89).

More sophisticated approaches to the site of the lesion in mouse models of AML have indicated that disorders like acute promyelocytic leukemia for which there is evidence in humans that it may originate in a more differentiated progenitor, such as the granulocyte-monocyte colony-forming cell,[54] places the neoplastic event(s) in a much earlier multipotential (?stem) cell.[55] Indeed, some experts have concluded that all clonal myeloid neoplasms originate in a mutated lymphohematopoietic stem cell, whereas others do not feel the evidence is either consistent or conclusive and that either a stem cell or an early multipotential progenitor cell could be the site of the transformation.

QUANTITATIVENESS OF CLONAL MYELOID DISEASES

The mutational lesions of the primitive hematopoietic multipotential cell compartment are qualitative in the sense that a distinct alteration from normal is seen in the function of that cell pool. The alteration reflects an acquired change in the genome of one primitive hematopoietic cell. This qualitative change, however, is such that the mutant multipotential cell can express all or some of the normal differentiation and maturation options. This expression can mimic closely the differentiation (commitment) and maturation expected of normal hematopoietic cells, as occurs in CML, essential thrombocythemia, and polycythemia vera. Most cases tend to conform to readily recognized patterns, but the opportunity for a large number of variations on the most common themes is possible. Thus, some mixed and "in-between" syndromes occur in which features of ineffective hematopoiesis and myeloproliferation of different cell lineages are present. For example, extreme thrombocytosis, usually confined to essential thrombocythemia, may accompany CML, primary myelofibrosis, or clonal bicytopenia with thrombocytosis. Erythrocytosis may rarely accompany CML. Atypical myeloproliferative syndromes or other clonal myeloid diseases may have mixtures of anemia, granulocytopenia, and thrombocytosis or of anemia, granulocytosis, and thrombocytopenia rather than pancytopenia. Qualitative abnormalities of red cell, granulocyte, or platelet structure or function may be more or less prominent in a given patient. For example, qualitative abnormalities of erythroblast development may result in acquired α-thalassemia (acquired hemoglobin H disease), especially in patients with primary myelofibrosis, or occasionally other clonal myeloid diseases. In AML, unusual patterns of phenotypic expression occur frequently. For example, prominent leukemic erythroblasts and monocytes or eosinophils and monocytes may be seen in patients. So much opportunity for variation in disease expression exists among patients with AML that observation of patients in whom the phenotype of their leukemic cells is identical to the phenotype of other patients is unusual. Choice of treatment is little affected by these

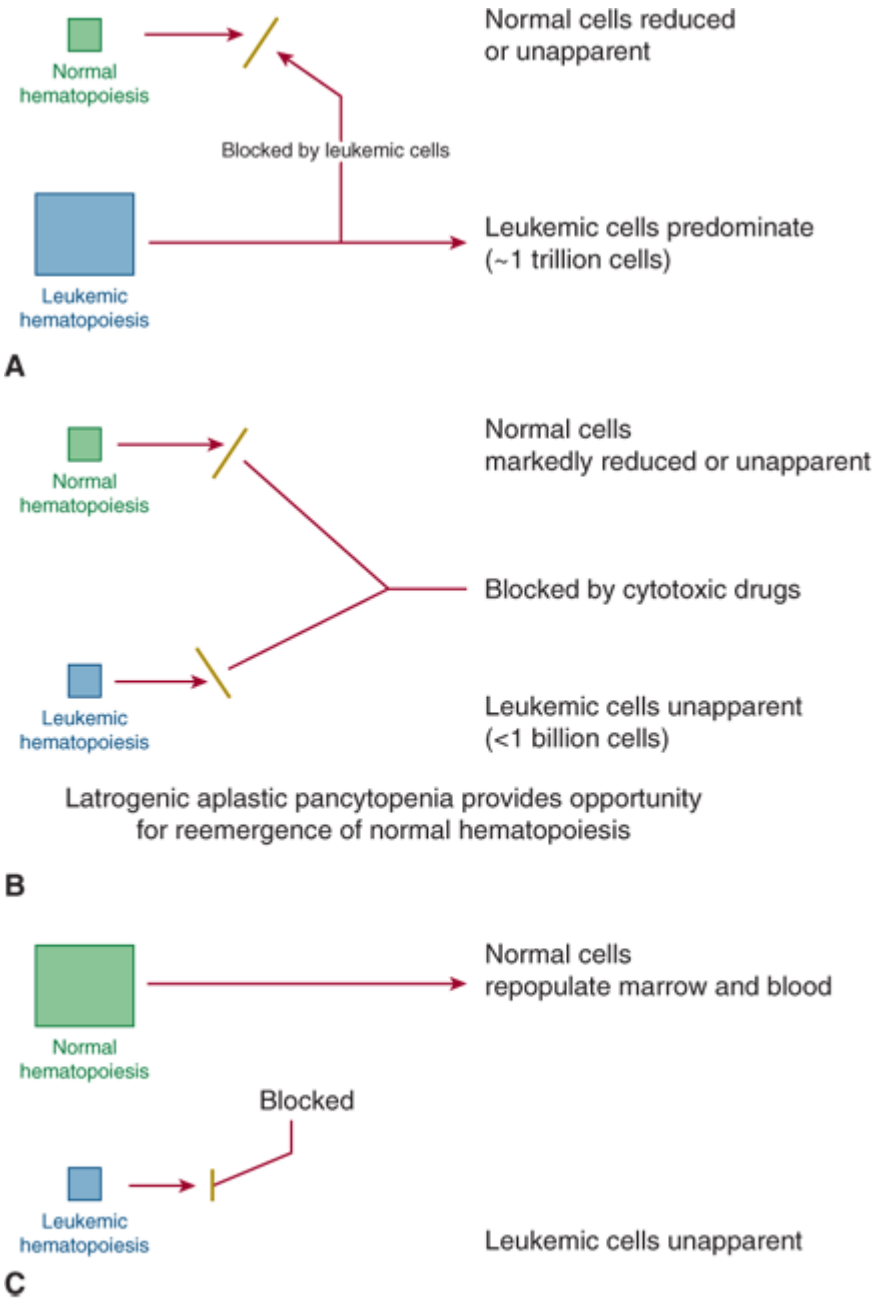
variations. Decisions about whether to treat and which drugs to use are greatly influenced by whether a patient has a chronic, subacute, or acute clonal myeloid disease; by the rate of progression of the disease; by the extent of the leukemic blast cell infiltrate; by the cytogenetic findings; and by the severity of the cytopenias. The experienced diagnostician and therapist usually can identify variants as a clonal myeloid disorder and can manage the disorder as dictated by their manifestations regardless of their precise subclassification.

INTERPLAY OF CLONAL AND POLYCLONAL HEMATOPOIESIS

Although potentially curative chemotherapy of myelogenous leukemia was introduced in the mid-20th century to kill "the last leukemic cell," two important factors were not explicitly appreciated. The first was whether residual normal stem cells coexisted in marrow to restore polyclonal (normal) hematopoiesis if ablation of the leukemia was accomplished. The second was whether, given the estimates of 1 trillion leukemic cells in a patient, the therapist had to eliminate all the leukemic cells to achieve a cure. A corollary of the latter was whether the disease was the result of a leukemic stem cell and, if so, was the undifferentiated replicates of the leukemic stem cell the only cells that mattered, ultimately, in the eradication process. We know that remissions result from sufficient suppression of the leukemic population by intensive chemotherapy to permit restitution of polyclonal hematopoiesis by normal stem cells (Fig. 83–4).[56] Why monoclonal leukemic hematopoiesis is so difficult to subdue, even temporarily, with intensive chemotherapy (pre–tyrosine kinase therapy) in the chronic myeloid neoplasms (e.g., CML) compared to the acute myeloid neoplasms (AML) is unclear. Prolonged remission (longer than 3 years) may occur in some cases of AML with late relapse occurring from the same clone, suggesting a new symbiotic relationship occurs after intensive therapy that suppresses the growth potential of leukemic cells for an extended period of time. A role for the patient's immune system in such protracted remissions has been hypothesized and forms the basis for attempts to manipulate cellular and innate immunity in an attempt to improve therapeutic results.

Figure 83–4.
Remission–relapse pattern of acute myelogenous leukemia. **A.** Acute myelogenous leukemia at diagnosis or in relapse. Monoclonal leukemic hematopoiesis predominates. Normal polyclonal stem cell function is suppressed. **B.** Following effective cytotoxic treatment leukemic cells are unapparent in marrow and blood. Severe pancytopenia exists as a result of cytotoxic therapy. The reduction in leukemic cells can release inhibition of normal polyclonal stem cell function. **C.** If reconstitution of normal hematopoiesis ensues, a remission is established and blood cells return to near normal as a result of the recovery of polyclonal hematopoiesis. This relapse–remission pattern has not been seen, generally, in the subacute and chronic myeloid leukemias treated with similar chemotherapy. Either it has not been possible to minimize the leukemic cell population with cytotoxic therapy to a point at which polyclonal hematopoiesis is restored or some other factors inhibit normal stem cell recovery. The principal exception is the effect of BCR-ABL1 inhibitor therapy in which suppression of BCR-ABL1–positive cells in CML can be achieved with return of polyclonal hematopoiesis. Uncommon examples of tyrosine kinase inhibitor responses in myeloid neoplasms with *PDGFR* or certain *KIT* mutations may also show this pattern. In a proportion of cases, BCR-

ABL1 transcripts (minimal residual disease) can be detectable along with normal, polyclonal hematopoiesis (mosaic hematopoiesis). *(Reproduced with permission from Lichtman MA: Interrupting the inhibiton of normal hematopoiesis in myelogenous leukemia: A hypothetical approach to therapy.* Stem Cells *18(5):304–306, 2000.)*



CLINICAL MANIFESTATIONS

DEFICIENCY, EXCESS, OR DYSFUNCTION OF BLOOD CELLS

Alterations in blood cell concentration are the primary manifestations of clonal hematopoietic disorders. The clinical manifestations of deficiencies or excesses of individual blood cell types are described in the chapters on clinical manifestations of disorders of erythrocytes (Chap. 34), granulocytes (Chap. 64), monocytes (Chap. 69), and platelets (Chap. 116).

Several clonal hematopoietic diseases frequently manifest as qualitative abnormalities of blood cells. Abnormal red cell shapes, red cell or granulocyte enzyme deficiencies, abnormal neutrophil granules, bizarre nuclear configurations, disorders of neutrophil chemotaxis, phagocytosis or microbial killing, giant platelets, abnormal platelet granules, and disturbed platelet function can occur in some patients with oligoblastic myelogenous leukemia and primary myelofibrosis. In oligoblastic myelogenous leukemia, the effects of severe cytopenia usually dominate. In primary myelofibrosis and essential thrombocythemia, functional platelet abnormalities may contribute to the hemorrhagic diathesis, especially if surgery or injury occurs. Paroxysmal nocturnal hemoglobinuria is a hematopoietic multipotential cell disease resulting from a somatic mutation of the *PIG-A* gene on the active X chromosome. The mutation causes a highly specific alteration in blood cell membranes, a deficiency in the glycosylphosphatidylinositol (GPI) anchor, with decreased cell-surface CD59, rendering the blood cells exquisitely sensitive to complement lysis. In its classic form, chronic hemolytic anemia is coupled with mild decreases in neutrophil and platelet counts but depressions in hematopoiesis often occur (hypoplastic marrow; Chap. 40). Patients with CML or polycythemia vera usually do not have clinically significant functional abnormalities of cells, although in polycythemia vera, neutrophils often are activated with heightened metabolic rates and enhanced phagocytosis.

Secondary clinical manifestations occur as a result of the proliferation and accumulation of the malignant (leukemic) cells.

EFFECTS OF LEUKEMIC BLAST CELLS

Extramedullary Tumors

Myeloid (granulocytic) sarcomas (also called *chloromas* or *myeloblastomas*) are discrete tumors of leukemic cells that form in skin and soft tissues, breast, periosteum and bone, lymph nodes, mediastinum, lung, pleura, gastrointestinal tract, gonads, urinary tract, uterus, central nervous system, and virtually any other site (Chap. 88).[57,58,59] They can develop in patients with AML or the accelerated phase of CML and, occasionally, may be the first manifestation of AML, preceding morphologic evidence of the disease in marrow and blood by months or, sometimes, years. AML with the t(8;21) and inv(16) has a predisposition to form myeloid sarcomas, although other AML types may also. Myeloid sarcomas can be mistaken for large cell lymphomas because of the similarity of the histopathology in biopsy specimens from soft tissues. In the past, approximately 50 percent of cases that occur in the absence of blood and marrow involvement initially were misdiagnosed, usually as lymphoma.[57] The presence of eosinophils or other granulocytes in the mass may arouse suspicion of a myeloid sarcoma; however, immunohistochemistry should be used on such lesions to identify myeloperoxidase, lysozyme, CD117, CD61, CD68/KP1, and other relevant CD markers of myeloid

cells. One of four histopathologic patterns usually is evident by immunocytochemistry: myeloblastic, monoblastic, myelomonoblastic, or megakaryoblastic.

More diffuse collections of leukemic promonocytes or monoblasts can invade the skin, gingiva, anal canal, lymph nodes, central nervous system, or other tissues of patients with AML of the monocytic subtype and may form tumors in those locations. Leukemic monocytes tend to mature to the point at which they develop many of the cytoplasmic and membrane features required for motility and tissue entry.[60,61,62] Moreover, leukemic monocytes proliferate and survive in tissues for long periods. Consequently, this AML phenotype has a higher frequency of overt infiltrative tissue lesions than do other forms of AML.

Extramedullary tumors may usher in the accelerated phase of CML. These tumors may be composed of myeloblasts or lymphoblasts, although in each case the Ph chromosome or the *BCR-ABL1* fusion is present in the cells, indicating the extramedullary Ph-positive lymphoblastomas are the tissue variant of the predisposition of CML to transform into a terminal deoxynucleotidyl transferase-positive lymphoblastic leukemia in approximately 30 percent of patients who enter blast crisis (Chap. 89).

Release of Procoagulants and Fibrinolytic Activators

Microvascular thrombosis is a feature of AML of the promyelocytic type, although thrombosis can occur in other forms of acute leukemia, especially in cases with elevated white cell counts or monocytic phenotypes.[63,64] The leukemic promyelocytes liberate tissue factor and other procoagulants, giving rise to disseminated intravascular coagulation, and annexin II, which augments conversion of plasminogen to plasmin and contributes to the activation of fibrinolysis (Chaps. 88, 129, and 135). Each mechanism contributes to hypofibrinogenemia and hemorrhage. Thrombin generation may mediate the microvascular thrombotic aspect of this process, which can occur in acute promyelocytic, acute monocytic, or acute myelomonocytic leukemia, either before or after cytotoxic treatment.[65,66] The increased fibrinolytic activity further complicates coagulopathy in patients with promyelocytic leukemia.

Large-vessel arterial thrombosis is very rare as a presenting feature or complication of leukemia but has occurred in the setting of hyperleukocytosis and as a presenting feature of acute promyelocytic leukemia.[67,68]

The plasma levels of protein C antigen, functional protein C, free protein S, and antithrombin are decreased in some patients with AML. Although these changes are particularly notable in acute promyelocytic leukemia, they occur occasionally in other morphologic variants of AML. The changes are not related to liver disease or white cell count.[69,70]

Hyperleukocytic Syndromes

A proportion of patients with AML (5 to 15 percent) and CML (10 to 20 percent) manifest extraordinarily high blood leukocyte counts.[71,72,73,74,75] These patients present special problems because of the effects of blast

cells in the microcirculation of the lung, brain, eye, ear, and penis, and the metabolic effects that result when massive numbers of leukemic cells in blood, marrow, and tissues are simultaneously killed by cytotoxic drugs. Cell concentrations greater than 100,000/μL (100×10^9/L) in AML and greater than 300,000/μL (300×10^9/L) in CML usually are required to produce such problems. In CML, the manifestations of hyperleukocytosis are usually reversed by cytoreduction and may not portend a poor outcome with anti–tyrosine kinase therapy. In AML, intracerebral hemorrhage and the impairment of pulmonary function are the most serious manifestations in predicting early death.[74,75] A respiratory distress syndrome attributed to pulmonary leukostasis occurs in some patients with acute promyelocytic leukemia after all-*trans*-retinoic acid therapy.[76] The syndrome is usually, but not always, associated with prominent neutrophilia.

The viscosity of blood is related to the total cytocrit and usually is not increased in hyperleukocytic leukemias because the reduced hematocrit compensates for increased leukocrit. This compensatory change is invariably present in AML. In CML there is a very close negative correlation of hematocrit with leukocrit, preventing an increase in bulk viscosity.[71] Occasional patients with hyperleukocytic CML who are transfused initially with red cells may have a blood viscosity increased above normal.

Pathologic studies of patients who have died with hyperleukocytosis have identified leukoocclusion and vascular invasion in small vessels of the lung, brain, or other sites. Because viscosity in the microcirculation is a function of the plasma viscosity and the deformability of individual cells in capillaries, leukocytes should transiently raise the viscosity in such small channels. Flow in microvascular channels decreases if poorly deformable blast cells enter capillary channels.[77] With high leukocyte counts, chronically reduced flow may reduce oxygen transport to tissues because the probability of leukocytes being in microchannels should increase as a function of white cell count. Moreover, trapped leukemic cells have an oxygen consumption rate that contributes to deleterious effects in the microcirculation. Leukocyte aggregation, leukocyte microthrombi, release of toxic products from leukocytes, endothelial cell damage, and microvascular invasion can contribute to vascular injury and flow impedance. Adhesive interactions between leukemic blast cells and endothelium may also be involved but have not been defined.

High leukemic blast cell counts in AML and CML may be associated with pulmonary, central nervous system, special sensory, or penile circulatory impairment (Table 83–3). Sudden death can occur in patients with hyperleukocytic acute leukemia as a result of intracranial hemorrhage.[74,75] Hyperleukocytosis can be treated initially with hydration, leukapheresis, and/or cytotoxic therapy, usually hydroxyurea (Chaps. 88 and 89). In patients with CML, leukapheresis reverses the hyperleukocytic syndrome and can reduce the extent of cytolysis-induced hyperuricemia, hyperkalemia, and hyperphosphatemia by reducing tumor cell mass before hydroxyurea therapy. Hydroxyurea may follow as, or soon after, the tumor cell burden is decreased. Unfortunately, the specific effect of leukapheresis, hydroxyurea therapy, or cranial irradiation in patients with hyperleukocytic AML on duration of survival appears to be negligible.[73,74,75]

Table 83–3.

Clinical Features of the Hyperleukocytic Syndrome

I. Pulmonary circulation
- A. Tachypnea, dyspnea, cyanosis
- B. Alveolar–capillary block
- C. Pulmonary infiltrates
- D. Postchemotherapy respiratory dysfunction

II. Predisposition to tumor lysis syndrome

III. Central nervous system circulation
- A. Dizziness, slurred speech, delirium, stupor
- B. Intracranial (cerebral) hemorrhage

IV. Special sensory organ circulation
- A. Visual blurring
- B. Papilledema
- C. Diplopia
- D. Tinnitus, impaired hearing
- E. Retinal vein distention, retinal hemorrhages

V. Penile circulation
- A. Priapism

VI. Spurious laboratory results
- A. Decreased blood partial pressure of oxygen (P_{O2}); increased serum potassium
- B. Decreased plasma glucose; increased mean corpuscular volume, red cell count, hemoglobin, and hematocrit

THROMBOCYTHEMIC SYNDROMES: HEMORRHAGE AND THROMBOPHILIA

Hemorrhagic or thrombotic episodes can develop during the course of essential thrombocythemia or thrombocythemia associated with other clonal myeloid diseases.[76,77,78] Arterial vascular insufficiency and venous thromboses are the major vascular manifestations of thrombocythemia. Peripheral vascular insufficiency with gangrene and cerebral vascular thrombi can develop. Thrombosis of superficial or deep veins of the extremities occurs frequently.[79] Mesenteric, hepatic, portal, splenic, or penile venous thrombosis can ensue. Patients with essential thrombocythemia who have the *CALR* mutation have a significantly lower risk of thrombotic disease than those with a *JAK2* or *MPL* mutation.[80] Hemorrhage is an occasional manifestation of thrombocythemia and can occur concomitantly with thrombotic episodes. Gastrointestinal hemorrhage and cutaneous hemorrhage, the latter especially after trauma, happen most frequently, but bleeding from other sites also can result (Chap. 85).

Procoagulant factors, such as the content of platelet tissue factor and blood platelet neutrophil aggregates, are more frequent in patients with essential thrombocythemia than normal subjects and are more frequent among patients with the *JAK2*^{V617F} mutation than patients with the wild-type gene.[79,81]

Thrombotic complications occur in approximately 40 percent of patients with polycythemia vera.[79,82] The presence of homozygosity for the *JAK2* mutation as a result of uniparental disomy in as many as one-third of patients with polycythemia vera increases the risk of thrombosis. Erythrocytosis and thrombocytosis may interact and cause hypercoagulability, especially in the abdominal venous circulation. A syndrome of splanchnic venous thrombosis associated with endogenous erythroid colony growth, the latter characteristic of polycythemia vera, but without blood cell count changes indicative of a myeloproliferative disease, has accounted for a high proportion of patients with apparent idiopathic hepatic or portal vein thrombosis.[83,84] These cases may have blood cells with the *JAK2* gene mutation without a clinically apparent myeloproliferative phenotype.[85]

Nearly half of patients with paroxysmal nocturnal hemoglobinuria have thrombosis, especially in the venous system. Thrombosis of the veins of the abdomen, liver, and other organs, characteristic complications of paroxysmal nocturnal hemoglobinuria, may result from a complex thrombophilic state related to nitric oxide depletion, formation of prothrombotic platelet microvesicles, the dysfunction of tissue factor pathway inhibitor, and other factors.[86,87] Thrombosis is more common in paroxysmal nocturnal hemoglobinuria (PNH) patients with the classical hemolytic syndrome than in those with the PNH-aplastic anemia hybrid (Chap. 40).

SYSTEMIC SYMPTOMS

Fever, weight loss, and malaise occur as early manifestations of AML. At the time of diagnosis, low-grade fever is present in nearly 50 percent of patients.[88] Although minor infections may be present, severe systemic infections are relatively uncommon at the time of AML diagnosis.[89] However, fever during cytotoxic therapy, when neutrophil counts are extremely low, nearly always is a sign of infection. Fever also may be a manifestation of the acute leukemic transformation of CML and can occur in patients with oligoblastic myelogenous leukemia (refractory anemia with excess blasts).

Weight loss occurs in nearly 20 percent of patients with AML.[89] Loss of well-being and intolerance to exertion may be disproportionate to the extent of anemia and may not be corrected by red cell transfusions. The pathogenesis of these effects is unknown.

METABOLIC SIGNS

Hyperuricemia and hyperuricosuria are common manifestations of AML and CML. Acute gouty arthritis and hyperuricosuric nephropathy are less common. If therapy is instituted without a reduction in plasma uric acid and without adequate hydration, saturation of the urine with uric acid can lead to precipitation of urate (gravel) and obstructive uropathy. If the uropathy is severe, urine flow can be obliterated, and renal failure

ensues. Hyponatremia can occur in AML, and in some cases results from inappropriate antidiuretic hormone secretion. Hyponatremia also can result from an osmotic diuresis of urea, creatinine, urate, and other substances released from blast cells and wasting muscles. Hypernatremia is rare but may be seen in cases with central diabetes insipidus. Hypokalemia is commonly seen in AML[89,90,91] and is thought to be caused by injury to the kidney by increased plasma and urine lysozyme and subsequent kaliuresis. Hypokalemia is related to excessive urinary potassium loss, but the correlation with lysozymuria is imperfect. Other mechanisms probably are responsible in most cases, including osmotic diuresis and tubular dysfunction. Kaliuretic antibiotics, often administered to patients with AML, may accentuate the hypokalemia. Hyperkalemia is very unusual, but may be seen with tumor lysis syndrome. Hypercalcemia occurs in occasional patients with AML. Several causes have been proposed, including bone resorption as a result of leukemic infiltration. This explanation is in keeping with the normal serum inorganic phosphate in most patients. Occasional patients with hypercalcemia, and hypophosphatemia can have ectopic parathyroid hormone secretion by leukemic blast cells. Hypophosphatemia also can occur because of rapid utilization of plasma inorganic phosphate in some cases of myelogenous leukemia with a high blood blast cell count and a high fraction of proliferative cells. Hyperphosphatemia is uncommon, except as a reflection of the tumor lysis syndrome. Approximately 10 percent of persons with AML show varying degrees of tumor lysis syndrome in the week after onset of therapy, reflected in at least doubling of baseline creatinine, and increases in serum phosphate (>1.6 mmol/L [>5 mg/dL]), uric acid (>416 mmol/L [>7mg/dL]), or potassium (>5 mmol/L [>5 mEq/L]).[92] Hypomagnesemia is common as a result of low intake coupled with gastrointestinal loss and a shift of magnesium to the intracellular compartment.

Acid–base disturbances occur in approximately 25 percent of patients, the majority having respiratory or metabolic alkalosis.[91] The latter may be secondary to volume depletion, upper gastrointestinal fluid loss, and hypokalemia. Lactic acidosis also has been observed in association with AML, although the mechanism is obscure. True hypoxia can result from the hyperleukocytic syndrome as a consequence of pulmonary vascular leukostasis (see also "Factitious Laboratory Results" below).

Increased serum concentrations of lipoprotein (a) and decreased concentrations of both low-density and high-density lipoproteins have been observed in a high proportion of patients with AML.[93] The increased level of lipoprotein (a), which returns to normal after successful treatment, correlates with the presence of leukemic blast cells. Serum prolactin also is increased in some patients with AML.[94] Leukemic blast cells may be an ectopic source of this hormone.[94]

Colony-stimulating factor-1 is elevated in a variety of lymphoid and hemopoietic malignancies, including AML and CML.[95] The malignant cells have been proposed as the source of excess cytokine.

FACTITIOUS LABORATORY RESULTS

Elevations of serum potassium levels have resulted from the release of potassium from platelets or, less often, leukocytes in patients with myeloproliferative diseases and extreme elevations in those blood cell concentrations. If blood is collected in a tube that contains an anticoagulant and the plasma is removed after

high-speed centrifugation, the potassium concentration is normal. Glucose can be falsely decreased, especially because autoanalyzer techniques call for omission of glycolytic inhibitors such as sodium fluoride in collection tubes. Blood with high leukocyte counts, if it stands prior to separation of the plasma, may have a significant amount of glucose metabolism by leukocytes. Factitious hypoglycemia also can occur as a result of red cell utilization of glucose, especially in polycythemic patients. True hypoglycemia has been observed rarely in patients with leukemia. Arterial blood oxygen content also can be lowered spuriously as a result of *in vitro* utilization by large numbers of leukocytes, while the anticoagulated blood awaits measurement.

SPECIFIC ORGAN INVOLVEMENT

Clonal myeloid diseases lead to disturbances principally in marrow, blood, and spleen. Although clusters of cells may be found in all organs, major infiltrates and organ dysfunction are unusual. In AML and the acute blastic phase of CML, clinically significant infiltration of the larynx, central nervous system, heart, lungs, bone, joints, gastrointestinal tract, genitourinary tract, skin, or virtually any other organ can occur.

Splenomegaly

In AML, palpable splenomegaly is present in approximately one-third of cases, but usually is slight in extent. In the chronic myeloproliferative diseases, palpable splenomegaly is present in a high proportion of cases (polycythemia vera ~80 percent, CML ~90 percent, primary myelofibrosis ~100 percent). In essential thrombocythemia, splenic enlargement is present in approximately 30 percent of patients. A predisposition to silent splenic vascular thrombi, infarction, and subsequent splenic atrophy, analogous to that occurring in sickle cell anemia, is postulated as the cause of the lower frequency of splenic enlargement in essential thrombocythemia. Early satiety, left-upper-quadrant discomfort, splenic infarctions with painful perisplenitis, diaphragmatic pleuritis, and referred shoulder pain may occur in patients with splenomegaly, especially in the acute phase of CML and in primary myelofibrosis. In primary myelofibrosis, the spleen can become enormous, occupying the left hemiabdomen. Blood flow through the splenic vein can be so great as to lead to portal hypertension and gastroesophageal varices. Usually, reduced hepatic venous compliance also is present (Chap. 86). Bleeding and, occasionally, encephalopathy can result from portal–systemic venous shunts.

Marrow Necrosis

Extensive marrow necrosis, an uncommon event, can occur in any clonal myeloid disease, especially AML, and less often, primary myelofibrosis, CML, essential thrombocythemia, and polycythemia vera. Bone pain and fever are the most common initial findings. Anemia and thrombocytopenia are very common, as are nucleated red cells and myelocytes in the blood (leukoerythroblastic reaction).[96,97] Marrow aspiration does not result in a useful sample but biopsy early in the process usually shows hypocellularity with loss of marrow cell structural definition (blurred staining of residual cells), evidence of cell necrosis, gelatinous transformation of marrow, and, often, an amorphous eosinophilic material throughout. The mechanism is

thought to be microvascular dysfunction. Restitution of marrow and repopulation of hematopoietic tissue often may follow. The prognosis is a function of the underlying disease.

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