Acute Leukemias

DEFINITION OF LEUKEMIA

Leukemia is caused by the mutation of the bone marrow pluripotent or most primitive stem cells. This neoplastic expansion results in abnormal, leukemic cells and impaired production of normal red blood cells, leukocytes, and platelets. As the mutant cell line takes hold and normal hematopoiesis is inhibited, the leukemic cells spill into the peripheral blood and invade the reticuloendothelial tissue, specifically the spleen, liver, lymph nodes, and sometimes the central nervous system (CNS). The leukemic stem cells have abnormal growth and maturation capability. The mutant clone may show unique morphologic, cytogenetic, and immunophenotypic features that can be used to aid in the classification of the particular type of leukemia. Many leukemias have similar clinical features, but regardless of the subtype, the disease is fatal if left untreated.

COMPARING ACUTE AND CHRONIC LEUKEMIA

The initial evaluation of leukemia includes the following:

1. Noting the onset of symptoms
2. Analyzing the complete blood count (CBC) results
3. Observing the type of cells that predominate (cell lineage)
4. Assessing the maturity of cells that predominate Because leukemia is a disease of the bone marrow that causes normal bone marrow cell production to be crowded out as the abnormal, neoplastic cells take over, the CBC results commonly show a decreased RBC or anemia and a decrease in platelets or thrombocytopenia. The level of anemia and thrombocytopenia tends to be more severe in acute leukemia. Leukocytosis is a hallmark feature of chronic leukemia, and because the spleen also becomes a site of extramedullary (outside of the bone marrow) hematopoiesis, prominent hepatosplenomegaly is also most often associated with chronic leukemia.

The type of cell that predominates in the peripheral blood and the bone marrow is defined according to cell lineage as either myeloid or lymphoid. The myeloid stem cell gives birth to granulocytes, monocytes, megakaryocytes, and erythrocytes.. As described in subsequent sections of this chapter, myeloid leukemias can involve proliferation of any stage of these four cell lineslymphoid stem cell gives rise solely to lymphocytic lineage cells. Cell maturity can be used to separate the initial diagnosis between acute and chronic leukemias. When blasts or other immature cells predominate, the leukemia is classified as acute; when more mature cell types predominate, the leukemia is classified as chronic.

The onset of acute versus chronic leukemia is distinctly different. Acute leukemia has a quick onset, whereas chronic leukemia has a slow, insidious course and may be discovered on routine physical examination. Age is another factor that is often consistent in the different leukemic variants. Although acute leukemia may occur at any age, chronic leukemia is usually seen in adults. Using the cell lineage and the maturity of cells that predominate, leukemias can be categorized into the following four broad groups:

1. Acute myelogenous leukemias (AMLs)
2. Acute lymphoblastic leukemias (ALLs)
3. Chronic myelocytic leukemias (CMLs)
4. Chronic lymphocytic leukemias (CLLs)

Comparison of Characteristics of Acute and Chronic Leukemia

Characteristic	Acute Leukemia	Chronic Leukemia
Onset	Abrupt	Subtle
Morbidity	Months	Years
Age	All	Adults
WBC	Variable	Elevated
Predominant cells	Blasts and other immature white blood cells	Mature
Anemia, thrombocytopenia	Present	Variable
Neutropenia	Present	Variable
Organomegaly	Mild	Marked

ACUTE MYELOID LEUKEMIA AML

is a malignant, clonal disease that involves proliferation of blasts in bone marrow, blood, or other tissue. The blasts most often show myeloid or monocytic differentiation. Almost 80% of patients with AML have chromosome abnormalities, usually a mutation resulting from a chromosomal translocation (the transfer of one portion of chromosome to another). The translocation causes abnormal oncogene or tumor suppressor gene expression, and this results in uncontrolled cellular proliferation. Genetic syndromes and toxic exposure contribute to the pathogenesis in some patients.

Although the diseases grouped into the AML categories have similar clinical manifestations, the morphology, immunophenotyping, and cytogenetic features are distinct. Cytochemical stains are used along with morphology to help identify the lineage of the blast population. Electron microscopy may also be used to subclassify the various leukemias. Flow cytometry is increasingly used specifically to tag the myeloid or lymphoid antigens and classify the acute leukemias. Molecular studies are employed to establish clonality and identify translocations and gene mutations

Epidemiology

The incidence of AML increases with age, accounting for 80% of acute leukemias in adults and 15% to 20% of acute leukemias in children. When congenital leukemia (occurring during the neonatal period) does rarely occur, however, it is paradoxically AML rather than ALL, and it is often monocytic. The rate of occurrence of AML is greater in males than females, and there is an increased incidence in developed, more industrialized countries. Eastern European Jews have an increased risk of developing AML, whereas Asians have a decreased risk

Methods Useful in the Diagnosis of Acute Leukemia

Morphology	• Provides initial diagnostic information • Can often distinguish acute leukemia from a reactive process • Helps to distinguish AML, ALL, and myelodysplastic syndrome
Cytochemistry	• Rapid, readily accessible type of testing • Provides quick diagnostic information
Immunophenotyping	• Differentiates ALL from AML • Classifies subtypes of AML • Separates precursor B-ALL from precursor T-ALL • Provides vital information for treatment decisions • Provides prognostic information • Detects minimal residual disease
Cytogenetics	• Classifies subtypes of AML and ALL • Provides prognostic information
Molecular studies	• Identifies translocation and gene mutations • Establishes clonality • Detects minimal residual disease

Conditions and Disorders with Increased Risk for Development of Acute Leukemia

Down syndrome

Klinefelter syndrome

Turner syndrome

Monosomy 7 syndrome

Fanconi's anemia

Wiskott-Aldrich syndrome

Neurofibromatosis

Familial aplastic anemia

Fraternal twins and nonidentical siblings

Combined immunodeficiency syndrome

Blackfan-Diamond syndrome

Aplastic anemia

Myeloma

Sideroblastic anemia

Acquired genetic changes

Translocations

Inversions

Deletions

Point mutations

Paroxysmal nocturnal hemoglobinuria

Transition from other hematopoietic diseases (myeloproliferative disorders)

Ionizing radiation

Alkylating agents

Cytotoxic drugs

Pesticide exposure

Solvents

Clinical Features

All of the signs and symptoms that occur so abruptly in patients with AML are caused by the infiltration of the bone marrow with leukemic cells and the resulting failure of normal hematopoiesis. These leukemic cells that invade the bone marrow are dysfunctional, and without the normal hematopoietic elements the patient is at risk for developing life-threatening complications of anemia, infection secondary to functional neutropenia, and hemorrhage from thrombocytopenia

Fatigue and weakness are the most common complaints that reflect the development of anemia. Pallor, dyspnea on exertion, heart palpitations, and a general loss of well-being have been described. Fever is present is about 15% to 20% of patients and may be the result of bacterial, fungal, and, less frequently, viral infections, or may result from the leukemic burden of cells on tissues and organs. Easy bruising, petechiae, and mucosal bleeding may be found secondary to thrombocytopenia. Other, more severe symptoms related to decreased platelet counts that occur less commonly are gastrointestinal or genitourinary tract symptoms and CNS bleeding. CNS infiltration with high

numbers of leukemic cells has been reported in 5% to 20% of children and approximately 15% of adults with AML.

- Headache, blindness, and other neurologic complications are indications of meningeal involvement.
- Leukemic blast cells circulate through the peripheral blood and may invade any tissue.
- Extramedullary hematopoiesis is common in monocytic or myelomonocytic leukemias.
- Organs that were active in fetal hematopoiesis may be reactivated to produce cells when stressed by the poor performance of the overladen leukemic bone marrow. Hepatosplenomegaly and lymphadenopathy may occur but are not as prominent as in the chronic leukemias.
- Skin infiltration is very characteristic in monocytic leukemia, particularly gum infiltration that is termed gingival hyperplasia. When leukemic cells crowd the bone marrow of the long bones, joint pain may be produced.

Clinical Findings in Acute Leukemia

Pathogenesis	Signs and Symptoms
Bone marrow infiltration	
Neutropenia	Fever, infection
Anemia	Pallor, dyspnea, lethargy
Thrombocytopenia	Bleeding, petechiae, ecchymosis, intracranial hematoma, and gastrointestinal or conjunctival hemorrhage (rare)
Medullary infiltration	
Marrow	Bone pain and tenderness, limp, arthralgia
Extramedullary infiltration	
Liver, spleen, lymph nodes, thymus	Organomegaly
CNS	Neurologic complications including dizziness, headache, vomiting, alteration of mental function
Gums, mouth	Gingival bleeding and hypertrophy

Laboratory Features

Peripheral Blood and Bone Marrow Findings CBC and examination of peripheral blood smear are the first steps in the laboratory diagnosis of leukemia. Blood cell counts are variable in patients with AML. WBC may be normal, increased, or decreased. It is markedly elevated (greater than 100 * 109/L cells) in less than 20% of cases. Conversely, WBC is less than 5.0 * 109/L, with an absolute neutrophil count of less than 1.0 * 109/L, in about half of patients at the time of diagnosis. Blasts are usually seen on the peripheral smear, but in leukopenic patients, the numbers may be few and require diligent search to uncover. Cytoplasmic inclusions known as Auer rods are often present in a small percentage of the myeloblasts, monoblasts, or promyelocytes that occur in the various subtypes of AML. Auer rods are elliptical, spindlelike inclusions composed of azurophilic granules. Nucleated red blood cells may be present, as well as myelodysplastic features, including pseudohyposegmentation (pseudo–Pelger-Huët cells) or hypersegmentation of the neutrophils and hypogranulation

Anemia is a very common feature resulting from inadequate production of normal red blood cells. The reticulocyte count is usually normal or decreased. Red blood cell anisopoikilocytosis is mildly abnormal, with few poikilocytes present. Thrombocytopenia, which can be severe, is almost always a feature at diagnosis. Giant platelets and agranular platelets may be seen. Disseminated intravascular coagulation (DIC) is most commonly associated with the type of AML known as acute promyelocytic leukemia (APL). DIC is caused by the release of tissue factor–like procoagulants from the azurophilic granules of the neoplastic promyelocytes,

Clinical features

1. The mean age at diagnosis is 72 years, with only 15% of cases before 50 years of age. The male : female ratio is approximately 2 : 1.

2. Over 80% of cases are diagnosed from the results of a routine blood test, usually taken for another reason.

3. Enlargement of cervical, axillary or inguinal lymph nodes is the most frequent clinical sign. The nodes are usually discrete and non-tender.

4. Features of anaemia may be present and patients with thrombocytopenia may show bruising or purpura.

5. Splenomegaly and, less commonly, hepatomegaly are common in later stages.

6. Immunosuppression is often a significant problem resulting from hypogammaglobulinaemia and cellular immune dysfunction. Early in the disease course bacterial infections, such as sinus and chest infections, predominate but with advanced disease viral infections, especially herpes