Leukemia (Blood Cancer) — Classification and Typification

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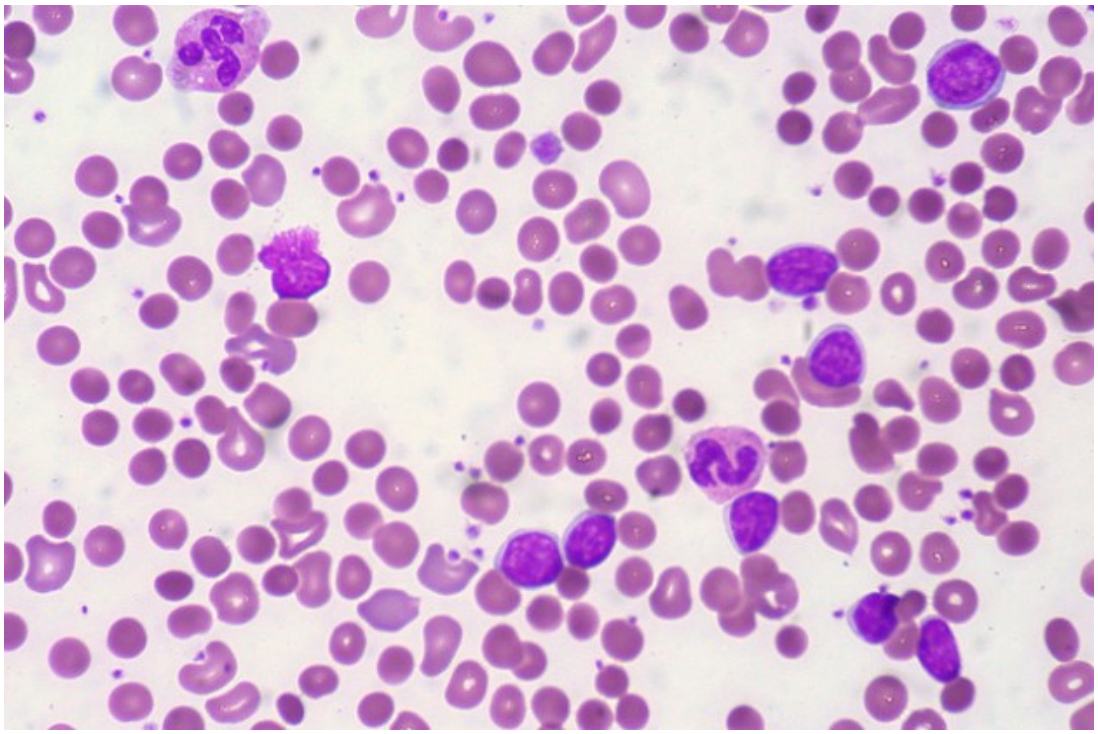
When the physicist and Nobel Prize winner Marie Curie died in 1934, her white blood cell count was found to be very high. During her work as a researcher and the years of contact with radioactive substances, she had developed leukemia. The various forms of leukemia and their causes are summarized in this article.



Leukemia and its Progression

Leukemia is defined as cancer that affects the bone marrow and blood. It occurs when the **precursor cells of the leukocytes** degenerate in the bone marrow. These cells begin to proliferate uncontrollably and are washed out into other **lymphatic organs** and the **blood** leading to two consequences. First, there is an increase in the size of the affected organs, such as the lymph nodes and **spleen,** and then, the precursors of normal **blood cells are displaced in the bone marrow**. This series of events leads to anemia, **thrombocytopenia,** and granulocytopenia with corresponding consequences such as weakness, hypoxia, bleeding tendency, and susceptibility to infections.

Note: Leukemia is the pathological proliferation of the precursor cells of the WBC in the bone marrow with a displacement of the precursors of other blood cells.

Acute Leukemia

This condition has the following hallmarks:

- Disease of neoplastic leukocytes
- Predominance of myeloblasts or lymphoblasts
- **Disease defined by > 20% ‘blasts’ in the bone marrow**
- Symptoms due to marrow failure secondary to leukemic infiltration causing pancytopenia—anemia, leukopenia, and thrombocytopenia

Etiology

- Chromosomal abnormalities (e.g., Down syndrome)
- Ionizing radiations
- Exposure to chemicals
- Use of topoisomerase inhibitors (chemotherapy)
- Age

Cancer is caused by DNA damage that leads to uncontrolled cell growth either by increasing the chemical signals that cause growth (proto-oncogenes) or by interrupting the chemical signals, such as tumor suppressor genes that control growth.

Hematopoiesis

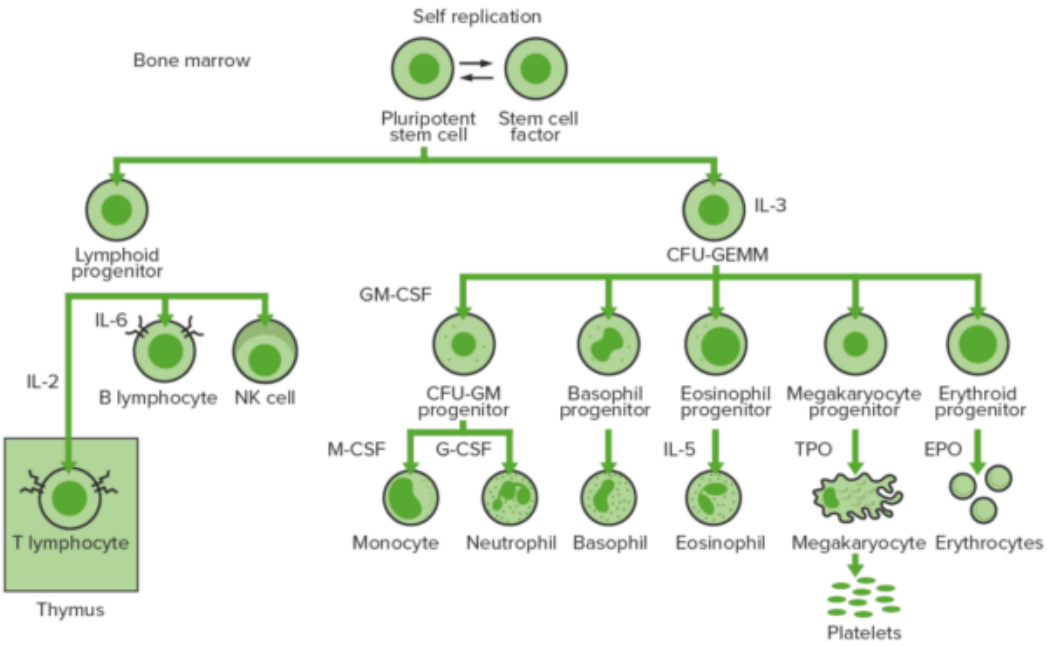


Image: Hematopoiesis. By Lecturio

Classification of Leukemia

Leukemia can be classified as acute or chronic, based on the **speed of progression of the condition** and the **prevailing cell type** (leukemic or lymphatic). It is also possible to characterize leukemia based on whether or not the leukocyte count is altered (leukemic or aleukemic). The aleukemic form, i.e. without abnormal leukocytes in the

blood, occurs only in the acute and not in the chronic form. Based on this information, the four forms of leukemia are described in the subsequent sections.

Acute lymphocytic leukemia (ALL)

ALL is the **most common type of leukemia in children,** which shows a peak incidence at 2–5 years of age (in about 80% of cases). This variant of leukemia may also occur in the elderly. The cause is usually unclear; however, additional genetic syndromes, such as trisomy 21, and chemical and environmental toxins, are known to increase the risk.

The symptoms are secondary to the typical changes that occur in the displacement of the other 'healthy' blood series in the bone marrow. Infections due to granulocytopenia, weakness, and performance decline due to anemia are frequent. Additionally, mucosal bleeding caused by thrombocytopenia is a common occurrence. In children, especially, the neoplastic leukocytes can infiltrate the skin and central nervous system leading to cranial nerve paralysis and headaches (leukemic meningitis).

ALL has several subtypes, thereby necessitating diagnostic **immunophenotyping,** which involves the determination of the surface markers of the leukocytes. Not only the success of therapy but also the survival of the individual depends on the subtype. Children have a higher survival probability than adults.

In 2008, the World Health Organization (WHO) defined therapeutically distinct categories based on the immunophenotyping of lymphocytes. Based on the surface markers, these three categories are as follows:

- B cell ALL
- Burkitt ALL (corresponds to ALL-L3)
- T cell ALL

This subtyping helps determine the prognosis and the most appropriate treatment in treating ALL. It is substantially amplified by cytogenetics and molecular diagnostics.

1. Acute lymphoblastic leukemia
    - i. **Precursor B** acute lymphoblastic leukemia. Cytogenetic subtypes:
        - t(12;21)(p12;q22) (or TEL/AML-1 fusion) = 21% most common; best prognosis
        - t(1;19)(q23;p13) (or PBX/E2A fusion) = 4.8%
        - t(9;22)(q34;q11) (or ABL/BCR fusion) = 1.6%
        - t(4;11)(q21;q23) (or V/MLL fusion) = 1.6%; most common in children < 12 months and presents poor prognosis
    - ii. **Precursor T** acute lymphoblastic leukemia
2. **Burkitt** leukemia [formerly classified as **French-American-British (FAB)**-L3]
3. **Biphenotypic** acute leukemia

Owing to the variation in disease progression of ALL, there is **no standard treatment modality**. Based on the risk factors (e.g., genetic or immunophenotypic characteristics), patients are divided into **study groups and treated accordingly**. In addition to the symptomatic treatment of anemia and other presenting conditions, chemotherapy is

useful in reducing the production of abnormal cells. In certain cases, including unsuccessful chemotherapy, bone marrow transplantation by a foreign donor can also be considered.

Note: Common in children; many subtypes (immunophenotyping necessary); symptoms of bone marrow failure (anemia, thrombocytopenia, granulocytopenia) most common; therapy in study groups; intrathecal prophylaxis important.

Acute myelogenous leukemia (AML)

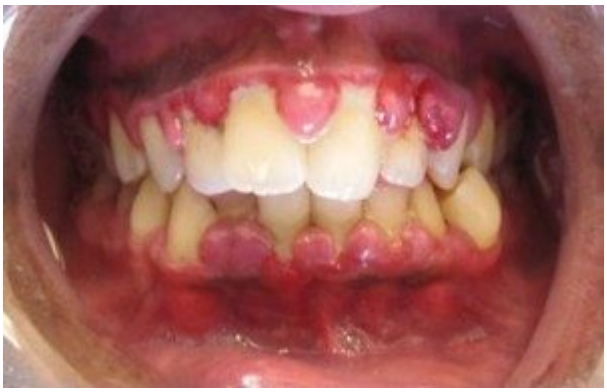


Image: Gingival Hyperplasia. By Lesion, License: CC BY-SA 3.0

The causes of acute myelogenous leukemia are also often unclear. The known risk factors are **ionizing radiations** and exposure to benzene. AML is an acute form of leukemia in adults, affecting especially **those in the sixth decade of life and older**. The median age at diagnosis is 63 years. Like ALL, this disease is characterized by symptoms of bone marrow failure. The mutated cell is the myeloid stem cell or the myeloid blast cell, both precursors of the monocyte and granulocyte. A rare, but typical manifestation of AML is gingival hyperplasia.

While a diagnosis of AML is possible after examination of the peripheral blood smear when there are **circulating leukemic blasts**, a definitive diagnosis usually requires a **bone marrow aspiration and biopsy**. AML is subdivided into cytomorphological subtypes, designated as M0 to M7, using the older **FAB classification**. This system requires the presence of > 30% of the peripheral blood or bone marrow blasts.

Type	Name	Cytogenetics	Percentage of adults with AML
M0	Acute myeloblastic leukemia, minimally differentiated		5%
M1	Acute myeloblastic leukemia, without maturation		15%
M2	Acute myeloblastic leukemia, with granulocytic maturation	t(8;21)(q22;q22), t(6;9)	25%
M3	Promyelocytic or acute promyelocytic leukemia (APL)	t(15;17)	10%
M4	Acute myelomonocytic leukemia	inv(16)(p13q22), del(16q)	20%
M4eo	Myelomonocytic together with bone marrow eosinophilia	inv(16), t(16;16)	5%
M5	Acute monoblastic leukemia (M5a) or acute monocytic leukemia (M5b)	del (11q), t(9;11), t(11;19)	10%

M6	Acute erythroid leukemias, including erythroleukemia (M6a) and pure erythroid leukemia (M6b) (very rare)		5%
M7	acute megakaryoblastic leukemia	t(1;22)	5%

According to the widely used **WHO** criteria, the diagnosis of AML is established by demonstrating the involvement of **> 20% of the blood, bone marrow, or both by leukemic myeloblasts**, except in the three best prognosis forms of acute myeloid leukemia with recurrent genetic abnormalities t(8;21), inv(16), and t(15;17), in which the presence of the genetic abnormality is diagnostic, irrespective of the blast percent. In approximately 30% of cases, microscopic **Auer rods** are observed in the precursor cells of the leukocytes, called blasts, which is characteristic of AML.

AML has been cured in 35–40% of individuals who are < 60 years of age and in 5–15% who are > 60 years of age. The elderly population, who are unable to withstand intensive chemotherapy, have an average survival of 5–10 months.

In AML, a condition called ‘leukemic hiatus’ is observed, during which there is a lack of the intermediate developmental stages of the myeloid series. This characteristic is absent in chronic myelogenous leukemia.

As in the case of ALL, intensive chemotherapy aimed at blast suppression is considered, with the option of stem cell transplantation. Recurrence is more common in AML than in ALL; therefore, the overall survival is relatively low (35%) without transplantation.

Note: Common in adults, especially the elderly; FAB classification; Auer rods in blasts; leukemic hiatus; high recurrence rate

Chronic lymphocytic leukemia (CLL)

CLL is the **most common form of leukemia** that mainly affects the **elderly**. Although it is not curable, it can be well managed. The cause is a monoclonal disorder characterized by a progressive accumulation of functionally incompetent **B cell** lymphocytes in the bone marrow, which leads to their massive proliferation. The displacement of other mature B lymphocytes leads to increased susceptibility to infections, autoimmune diseases, and tumors. There are familial clusters of CLL, suggesting a genetic defect.

The characteristic presenting feature of CLL is **lymph node swelling**, which is often the first symptom. In addition, cutaneous lesions are observed. The blood count and the number of affected lymph node stations are used for therapeutic planning and to determine the prognosis. The hepatic and splenic lymph nodes are also considered during evaluation.

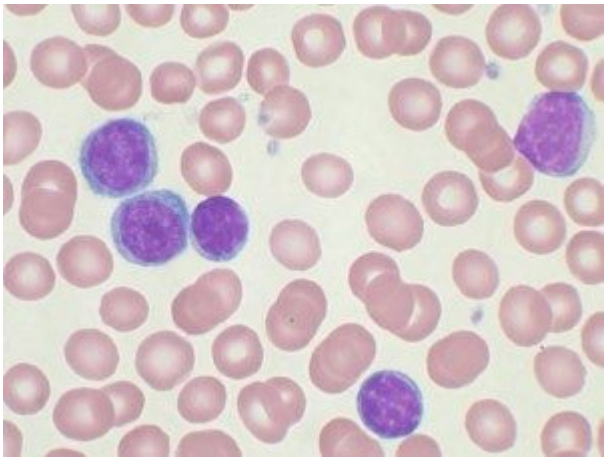


Image: Blood Smear in CLL. By VashiDonsk, License: CC BY-SA 3.0

Microscopy reveals typical **Gumprecht's nuclear shadows,** also called '**smudge cells.'** These are lymphocytes that burst when the blood streaks on the cover glass, as they are more fragile than the healthy cells. CLL is **slow** and rather benign; thus, aggressive therapy is generally not considered.

Note: Most common type of leukemia affecting the elderly; B cell proliferation due to loss of apoptosis; lymph node swelling; non-aggressive therapy.

Chronic myelogenous leukemia (CML)

Chronic myelogenous leukemia affects individuals in their **middle ages**. The disease mechanism involves the degeneration of the blood-forming stem cells, resulting in an increase in the **granulocytes**. CML is characterized by the presence of the **Philadelphia chromosome**, which originates from the long arm (q) of chromosomes 9 and 22 by reciprocal translocation [represented as t(9;22)(q34;q11.2)]. This translocation involves the ABL1 gene in chromosome 9 and the BCR gene in chromosome 22 in 90% of patients with CML; therefore, it is useful in diagnosing CML.

As a result of this translocation, the chromosome looks smaller than its homologous chromosome. Thus, this abnormality can be detected using routine cytogenetics. The fusion gene, BCR-ABL1, can be detected using fluorescent *in situ* hybridization as well as polymerase chain reactions.

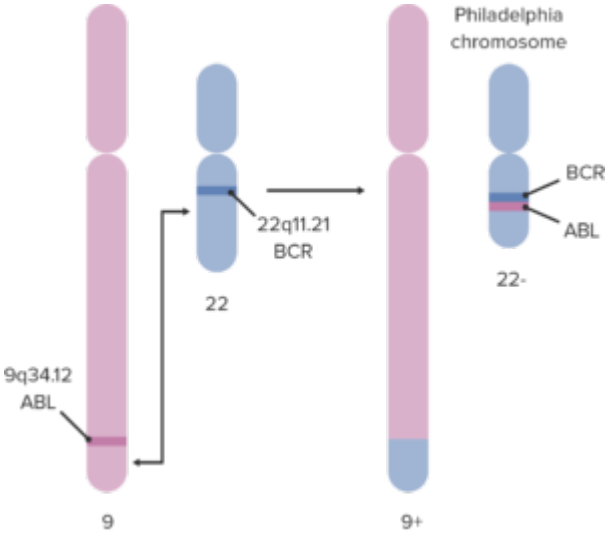


Image: Schematic of the Formation of the Philadelphia Chromosome. By Lecturio

Since the ABL gene carries a domain that can add phosphate groups to tyrosine residues (a tyrosine kinase), the BCR-ABL fusion gene is also a tyrosine kinase. The BCR-ABL protein interacts with the interleukin-3 beta c receptor subunit. The BCR-ABL transcript is continuously active and does not require activation by other cellular messaging proteins. In turn, BCR-ABL activates a cascade of proteins that controls the cell cycle, speeding up cell division. Moreover, the BCR-ABL protein inhibits DNA repair, causing genomic instability and rendering the cells more susceptible to developing further genetic abnormalities. The action of the BCR-ABL protein is the pathophysiological cause of CML.

CML is divided into **three phases.** In the stable phase, there are none or very few symptoms, and leukocytosis and splenomegaly may occur. In the subsequent acceleration phase, symptoms, such as fever, night sweat, and weight loss are experienced, and more than 10% of blasts are detected. In the third phase, there is a **blast crisis**, which is similar to acute leukemia. The only cure for CML was stem cell transplant, until the advent of antibody therapy using imatinib.

Note: Granulocyte expansion; Philadelphia chromosome; three-phase course with blast crisis; stem cell transplantation as a cure

The Process of Typification

During typification, the **tissue characteristics** of an individual, including the HLA (human leukocyte antigen) characteristics, are recorded. HLAs are polypeptides that are located on leukocytes. HLA typing is used to match patients and donors for bone marrow or cord blood transplants to reduce the chances of **rejection**.

Registering as many people as possible with different tissue traits increases the probability for patients finding a **suitable donor**.

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Notes