Leukemia (Blood Cancer) — Classification and Typification

When the physicist and Nobel Prize winner Marie Curie died in 1934, her blood was flooded by white blood cells. During her work as a researcher and the years of contact with radioactive substances, she had developed leukemia. There are various causes and forms for the disease, which is also known as blood cancer. Learn here about these and you will be well versed in the popular examination topic Leukemia.

This Disease Mechanism Leads to Leukemia

Leukemia occurs when the **precursor cells of the leukocytes**, i.e., the WBC, degenerate in the bone marrow. They begin to proliferate uncontrollably and are washed out into other **lymphatic organs** and the **blood** leading to 2 consequences. Firstly, the flooded organs such as lymph nodes and **spleen** greatly increase in size, and secondly, the precursors of normal **blood cells are displaced in the bone marrow**. This mechanism leads to anemia, **thrombocytopenia**, and granulocytopenia with corresponding consequences such as weakness, hypoxia, a tendency to bleed, and susceptibility to infections.

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

- Disease of neoplastic leukocytes
- Predominance of immature forms, especially blasts (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 radiation
- Chemical exposure
- Topoisomerase agents (chemotherapy)
- Age

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

Hematopoiesis

Classification of Leukemia

Leukemia can be classified according to their rate of development (acute or chronic) and the prevailing cell type (leukemic or lymphatic). It is also possible to characterize whether the leukocyte count in the blood is altered or not (leukemic or aleukemic). The aleukemic form, i.e. without abnormal leukocytes in the blood, occurs only in the acute forms, not in the chronic forms. Based on this classification, there are 4 forms of
Acute lymphocytic leukemia (ALL)

Acute lymphocytic leukemia is the most common type of leukemia in children, with a peak incidence at 2–5 years of age (about 80%). Another peak occurs in the elderly. The cause is usually unclear, but additional genetic syndromes such as trisomy 21, chemical and environmental toxins 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. There are frequent infections due to granulocytopenia, weakness, and performance decline due to anemia and mucosal bleeding caused by thrombocytopenia. Especially in children, the leukemia cells can also infiltrate the skin and central nervous system, leading to brain nerve paresis and headache (leukemic meningitis).

ALL is distinguished by the fact that there are many different subtypes, which is why diagnostic immunophenotyping is necessary. It is a measurement of the surface markers of the leukocytes. Not only the therapy but also the survival depends on this subtype. Children have a higher survival probability than adults.

In 2008, the World health organization (WHO) scheme identified 3 therapeutically distinct categories. These are identified by immunophenotyping of surface markers of the abnormal lymphocytes:

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 poor prognosis
   - ii. **Precursor T** acute lymphoblastic leukemia

2. **Burkitt** leukemia (Former FAB-L3)
3. **Biphenotypic** acute leukemia

Because of the great variability of ALL, there is no uniform treatment. Above all, children and adolescents are treated in the course of studies. Depending on the risk factors (e.g., genetic or immunophenotypic characteristics), patients are divided into study groups. In addition to the symptomatic treatment of anemia and other symptoms, chemotherapy is attempted to reduce the production of the abnormal cells. In the case of
special risk or 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)

The causes of acute myelogenous leukemia are also often unclear. Known risk factors are **ionizing radiation** and exposure to benzene. It is the acute leukemia form of the adult, especially **older adults in the 6th 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, both precursors of the monocyte and granulocyte. A rare, but typical manifestation of this leukemia is gingival hyperplasia.

While a diagnosis of AML is possible by examination of the peripheral blood smear when there are **circulating leukemic blasts**, a definitive diagnosis usually requires an adequate **bone marrow aspiration and biopsy**. AML is subdivided into cytomorphological subtypes, named M0 to M7, using the older **French-American-British (FAB) classification**. This system requires the presence of more than 30% of the peripheral blood or bone marrow blasts.

<table>
<thead>
<tr>
<th>Type</th>
<th>Name</th>
<th>Cytogenetics</th>
<th>Percentage of adults with AML</th>
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<tbody>
<tr>
<td>M0</td>
<td>acute myeloblastic leukemia, minimally differentiated</td>
<td></td>
<td>5%</td>
</tr>
<tr>
<td>M1</td>
<td>acute myeloblastic leukemia, without maturation</td>
<td></td>
<td>15%</td>
</tr>
<tr>
<td>M2</td>
<td>acute myeloblastic leukemia, with granulocytic maturation</td>
<td>t(8;21)(q22;q22), t(6;9)</td>
<td>25%</td>
</tr>
<tr>
<td>M3</td>
<td>promyelocytic or acute promyelocytic leukemia (APL)</td>
<td>t(15;17)</td>
<td>10%</td>
</tr>
<tr>
<td>M4</td>
<td>acute myelomonocytic leukemia</td>
<td>inv(16)(p13q22), del(16q)</td>
<td>20%</td>
</tr>
<tr>
<td>M4eo</td>
<td>myelomonocytic together with bone marrow eosinophilia</td>
<td>inv(16), t(16;16)</td>
<td>5%</td>
</tr>
<tr>
<td>M5</td>
<td>acute monoblastic leukemia (M5a) or acute monocytic leukemia (M5b)</td>
<td>del (11q), t(9;11), t(11;19)</td>
<td>10%</td>
</tr>
</tbody>
</table>
According to the widely used WHO criteria, the diagnosis of AML is established by demonstrating involvement of **more than 20% of the blood or bone marrow, or both by leukemic myeloblasts**, except in the 3 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 blast percent. In approx. 30%, microscopic **Auer rods** are seen in the precursor cells of the leukocytes, called blasts, which is characteristic of AML.

AML is cured in 35–40% of people under 60 years old and 5–15% over 60 years old. Older people who are not able to withstand intensive chemotherapy have an average survival of 5–10 months.

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

As with ALL, the therapy is intensive chemotherapy aimed at blast suppression, with the option of stem cell transplantation. In acute myelogenous leukemia, recurrence is more common than in ALL, which is why overall survival is relatively low (35%) without transplantation.

**Note:** Common in adults, especially older people; FAB classification; Auer rods in blasts; leukemic hiatus; high recurrence rate

### Chronic lymphocytic leukemia (CLL)

**Chronic lymphocytic leukemia** is the **most common form of leukemia**, which affects mainly **older people**. It is not curable but can be treated well. The cause is a monoclonal disorder characterized by a progressive accumulation of functionally incompetent B cell lymphocytes in the bone marrow, which leads to a massive proliferation of these cells. 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 of CLL is **lymph node swelling**, which is often the first symptom. In addition, skin changes may occur. The blood count and the number of lymph node stations affected are used for therapeutic planning and prognosis estimation, with liver and spleen, also being considered a large lymph node station.
In microscopy, **Gumprecht’s nuclear shadows** are typical, and they are also called ‘**smudge cells.’** These are lymphocytes that burst when the blood streaks on the cover glass since they are more fragile than healthy cells. CLL is **slow** and rather benign, which is why an aggressive therapy is generally not considered.

**Note:** Most common leukemia form; older people; B cell proliferation due to loss of apoptosis; lymph node swelling; gentle therapy.

### Chronic myelogenous leukemia (CML)

Chronic myelogenous leukemia affects people in **midlife.** Disease mechanism involves the degeneration of the blood-forming stem cell, with the result that excessive **granulocytes** are formed. CML is characterized by the **Philadelphia chromosome,** which originates from the long arm (q) of chromosomes 9 and 22 by reciprocal translocation and is written as t(9;22)(q34;q11.2). This translocation involves the ABL1 gene in chromosome 9 and the BCR gene on chromosome 22, found in 90% of cases with CML, and is useful in diagnosing the illness.

As a result of this translocation, the chromosome looks smaller than its homologous chromosome. Thus, this abnormality can be detected by routine cytogenetics, and the involved genes BCR-ABL1 can be detected by fluorescent in situ hybridization, as well as by polymerase chain reaction (PCR).

The diagram shows the cells that CML develop from:
Because ABL carries a domain that can add phosphate groups to tyrosine residues (a tyrosine kinase), the BCR-ABL fusion gene product is also a tyrosine kinase. The fused 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 control the cell cycle, speeding up cell division. Moreover, the BCR-ABL protein inhibits DNA repair, causing genomic instability and making the cell more susceptible to developing further genetic abnormalities. The action of the BCR-ABL protein is the pathophysiologic cause of chronic myelogenous leukemia.

The disease is divided into 3 phases: in the stable phase, there are none or very few symptoms, leukocytosis and splenomegaly can occur. In the subsequent acceleration phase, symptoms such as fever, night sweat, loss of weight, and more than 10% blasts are found in the blood. Finally, there is a blast crisis, which is like acute leukemia. The only curative therapy for CML is stem cell transplant, and the more recent therapy option is the antibody Imatinib.

**Note:** Granulocyte expansion; Philadelphia chromosome; a 3-phase course with blast crisis; stem cell transplantation as a cure

### Process of Typification

In a typification, the **tissue characteristics** of a person are recorded, consisting of the HLA (human leukocyte antigen) characteristics. These are polypeptides that are located on leukocytes. The HLA is decisive for histocompatibility, i.e. the compatibility of foreign tissues among one another, and thus, for the prevention of rejection.

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

### References


Foon, K., & Gale, R. (1987). Immunologic classification of lymphoma and lymphoid


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