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 a 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**, ie the white blood cells, degenerate in the bone marrow. They begin to proliferate uncontrollably and are washed out into other **lymphatic organs** and the **blood**. This has two consequences. Firstly, that the flooded organs such as lymph nodes and **spleen** greatly increase in size, and secondly, that the precursors of normal blood cells are displaced in the bone marrow. This mechanism leads to anemia, **thrombocytopenia** and granulocytopenia with the corresponding consequences (weakness, hypoxia, tendency to bleed, and susceptibility to infections).

**Note:** Leukemia = pathological proliferation of the precursor cells of the white blood cells in the bone marrow with 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 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 Leukemias

Leukemias 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, ie without abnormal leukocytes in the blood, occurs only in the acute forms, not in the chronic forms. On the basis of this classification, four forms result.
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 and chemical 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. These 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 (so-called Meningeosis leucaemica).

ALL is distinguished by the fact that there are many different subtypes, which is why diagnostic immunophenotyping is necessary. This is a measurement of the surface markers of the leukocytes. The therapy, but also the survival depends on this subtype. Children have a higher survival probability than adults.

In 2008, the World Health Organization scheme identified three therapeutically distinct categories. These are identified by immunophenotyping of surface markers of the abnormal lymphocytes:

- B-lymphoblastic 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 tests.

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 mos and poor prognosis
   
   - ii. Precursor T acute lymphoblastic leukemia

2. Burkitt’s leukemia. Synonyms: 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 the other symptoms, chemotherapy attempts to reduce production of the abnormal cells. In the case of a 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 life decade 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 presumptive diagnosis of AML can be made 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, by means of the older French-American-British (FAB) classification. This system requires the presence of more than 30% of the peripheral blood or bone marrow be blasts.

<table>
<thead>
<tr>
<th>Type</th>
<th>Name</th>
<th>Cytogenetics</th>
<th>Percentage of adults with AML</th>
</tr>
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<tbody>
<tr>
<td>M0</td>
<td>acute myeloblastic leukemia, minimally differentiated</td>
<td></td>
<td>5% [28]</td>
</tr>
<tr>
<td>M1</td>
<td>acute myeloblastic leukemia, without maturation</td>
<td></td>
<td>15% [28]</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% [28]</td>
</tr>
<tr>
<td>M3</td>
<td>promyelocytic, or acute promyelocytic leukemia (APL)</td>
<td>t(15;17)</td>
<td>10% [28]</td>
</tr>
<tr>
<td>M4</td>
<td>acute myelomonocytic leukemia</td>
<td>inv(16)(p13q22), del(16q)</td>
<td>20% [28]</td>
</tr>
<tr>
<td>M4eo</td>
<td>myelomonocytic together with bone marrow eosinophilia</td>
<td>inv(16), t(16;16)</td>
<td>5% [28]</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% [28]</td>
</tr>
<tr>
<td>M6</td>
<td>acute erythroid leukemias, including erythroleukemia (M6a) and very rare pure erythroid leukemia (M6b)</td>
<td></td>
<td>5% [28]</td>
</tr>
</tbody>
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Image: “Gingival hyperplasia” by Lesion. Licence: CC BY-SA 3.0
According to the widely used WHO criteria, the diagnosis of AML is established by demonstrating involvement of **more than 20% of the blood and/or bone marrow 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 blast percent. In approximately 30%, microscopic **Auer rods** are seen in the precursor cells of the leukocytes, called blasts, that are 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 the blood picture of AML one often finds a so-called **“Hiatus leucaemicus”**, which means a lack of the middle development stages of the myeloid series. This characteristic is absent in chronic myelogenous leukemia.

As with ALL, the therapy is an 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, older people, FAB classification, Auer rods in blasts, hiatus leucaemicus, 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 well treated. 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.

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 those cells are also called "smudge cells". These are lymphocytes, which 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 dispensed.

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

**Chronic myelogenous leukemia (CML)**

Chronic myelogenous leukemia affects people in the **middle age of life**. Disease mechanism is the degeneration of a blood-forming stem cell, with the result that excessive granulocytes are formed. Characteristic of the CML is the so-called **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 in chromosome 22. It is found in 90% of cases with CML and is diagnostic for the illness.

As a result of this translocation, the chromosome looks smaller than its homologue 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 PCR.

Diagram showing the cells CML can 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 3beta(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 three phases: in the stable phase there are no or very few symptoms, leukocytosis and splenomegaly can occur. In the subsequent acceleration phase, symptoms such as fever, night sweat, loss of weight (B-symptomatics) occur more frequently in the blood, 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, 3-phase course with blast crisis, stem cell transplantation as a cure

**Process of Typification**

For stem cell transplantation, one needs a suitable donor. In Germany, the non-profit organization **DKMS** (Deutsche Knochenmarkspenderdatei) lists potential stem cell donors in a card index also available internationally. Mapping is carried out by 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 are decisive for histocompatibility, i.e., the compatibility of foreign tissues among one another, and thus for the prevention of rejection.

By registering as many people as possible with different tissue traits, the probability for patients to find a suitable donor increases. For example, you can register on the DKMS website.

**Review Questions**

You will find the solutions below the questions.

1. In a 83-year-old woman, you notice lymph node swelling in the neck and armpits during a check-up. She also has a leukocytosis of 55,000 gpt/L and anemia. In the microscopy of the blood smear you see so-called Gumprecht’s nuclear shadows. The patient has no complaints, except for shortness of breath and diminished efficiency she attributes to their age and a femoral neck fracture 5 months ago. What is your preliminary diagnosis?

   A. ALL  
   B. AML  
   C. CML  
   D. CLL  
   E. Multiple Myeloma

2. You are a cardiologist and want to prescribe phenprocoumone to a 69-year-old man with atrial fibrillation. He tells you he takes imatinib and has been told to tell this when getting prescribed new medications because the drug has many interactions. Due to which disease is the man most likely to take this tyrosine kinase inhibitor?

   A. Chronic myelogenous leukemia  
   B. Colitis ulcerosa  
   C. CREST syndrome  
   D. Chronic lymphatic leukemia  
   E. Conn syndrome

2. Which cell trait is typical of the acute myeloid leukemia?

   A. Auer rods  
   B. Sternberg reed cells  
   C. Gumprecht nuclear shadows  
   D. Hela cells  
   E. Jacket cells

**References**


