Hematological malignancies

Leukemias and lymphomas

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Hematological malignancies

- **Leukemia**
  is a malignant proliferation of white blood cells (lymphoid cells [lymphocytes] or myeloid cells [granulocytes and monocytes]), in which the malignant cells appear in the peripheral blood

- **Lymphoma**
  is a malignant neoplasm of lymphocytes in lymph nodes and organs that grows as nodular masses. No malignant cells are detectable in blood
Genetic factors

- Chromosomal abnormalities are often found in patients with leukemias:
  - Philadelphia chromosome (Philadelphia translocation) is associated with chronic myelogenous leukemia (CML). It is the result of a translocation between chromosome 9 and 22. The presence of this translocation is a highly sensitive test for CML, since 95% of people with CML have this abnormality.
Genetic factors

- A number of chromosomal and genetic abnormalities are associated with leukemias:
  - Down syndrome (trisomy 21)
  - Klinefelter syndrome (karyotype 47,XXY)
  - Bloom syndrome (gene located at 15q26.1; genomic instability)
  - Fanconi anemia (15 genes found)
Immunological factors

- **Primary immunodeficiencies**
  - Wiskott–Aldrich syndrome (X-linked recessive disease)
  - Ataxia telangiectasia (Louis–Bar syndrome; gene located at 11q22.3)

- **Secondary immunodeficiencies**
  - cytotoxic agents
  - radiation therapy
  - organ transplantation
  - HIV
Exogenous factors

- Physical (ionizing radiation)
- Chemicals (benzene)
- Viruses (T-cell leukemia (HTLV-I), Epstein-Barr virus)
Leukemia

- **Leukemia** is a malignant tumor of the hematopoietic system with uncontrolled proliferation of atypical immature blood cells in bone marrow and other organs (lymph nodes, spleen, etc.)
Main features of leukemia

1. Proliferation of atypical clone of hematopoietic cells
2. They originate from the precursors of granulocytes, lymphocytes and monocytes, but are not able to differentiate into normal blood cells
3. Bone marrow is affected primarily
Bone marrow (BM)

- Normal
- In leukemia
Main features of leukemia

4. BM infiltration leads to suppression of
   - leukopoiesis (→ leukopenia)
   - thrombocytopenies (→ thrombocytopenia)
   - erythrogenesis (→ anemia)

5. Atypical cells are found in blood

6. Atypical cells infiltrate organs
Basic clinical signs

**Systemic**
- Weight loss
- Fever
- Frequent infections

**Psychological**
- Fatigue
- Loss of appetite

**Lungs**
- Easy shortness of breath

**Lymph nodes**
- Swelling

**Spleen and/or liver**
- Enlargement

**Muscular**
- Weakness

**Skin**
- Night sweats
- Easy bleeding and bruising
- Purplish patches or spots

**Bones or joints**
- Pain or tenderness
A. Neutrophil
B. Lymphocyte

A. Malignant myeloblasts
Basic pathology of leukemia

1. Leukemic infiltrates in the BM, liver, spleen, lymph nodes and other organs with their enlargement
Basic pathology of leukemia

2. The manifestations of anemia
   - extramedullar hemopoiesis
   - lipid distrophy
   - cardiovascular disorders

3. Necrotic processes in mucosa:
   - necrotic angina
   - stomatitis
   - gingivitis
   - ulcers in the stomach, intestines, etc.
4. hemorrhagic syndrome resulting from
   - vessel wall infiltration
   - thrombocytopenia and anemia
   - low fibrinogen
## Classification

Maturity of the malignant cells and clinical signs

<table>
<thead>
<tr>
<th></th>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoid</td>
<td>ALL</td>
<td>CLL</td>
</tr>
<tr>
<td>Myeloid</td>
<td>AML</td>
<td>CML</td>
</tr>
</tbody>
</table>

Origin of malignant cells
# French-American-British (FAB) AML classification

<table>
<thead>
<tr>
<th>Type</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>minimally differentiated acute myeloblastic leukemia</td>
</tr>
<tr>
<td>M1</td>
<td>acute myeloblastic leukemia, without maturation</td>
</tr>
<tr>
<td>M2</td>
<td>acute myeloblastic leukemia, with granulocytic maturation</td>
</tr>
<tr>
<td>M3</td>
<td>promyelocytic, or acute promyelocytic leukemia (APL)</td>
</tr>
<tr>
<td>M4</td>
<td>acute myelomonocytic leukemia</td>
</tr>
<tr>
<td>M4eo</td>
<td>myelomonocytic together with bone marrow eosinophilia</td>
</tr>
<tr>
<td>M5</td>
<td>acute monoblastic leukemia (M5a) or acute monocytic leukemia (M5b)</td>
</tr>
<tr>
<td>M6</td>
<td>acute erythroid leukemias, including erythroleukemia (M6a) and very rare pure erythroid leukemia (M6b)</td>
</tr>
<tr>
<td>M7</td>
<td>acute megakaryoblastic leukemia</td>
</tr>
</tbody>
</table>
French-American-British (FAB) AML classification

<table>
<thead>
<tr>
<th>M0 MYELOBLASTIC (minimally differentiated)</th>
<th>M1 MYELOBLASTIC (without maturation)</th>
<th>M2 MYELOBLASTIC (with maturation)</th>
<th>M3 MYELOCYTIC</th>
<th>M4 MYELOMONOCYTOBLASTIC (biphasic M1 and M5)</th>
<th>M5 MONOBLASTIC</th>
<th>M6 ERYTHROBLASTIC</th>
<th>M7 MEGAKARYOBLASTIC</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Image 1" /></td>
<td><img src="image2.png" alt="Image 2" /></td>
<td><img src="image3.png" alt="Image 3" /></td>
<td><img src="image4.png" alt="Image 4" /></td>
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<td><img src="image6.png" alt="Image 6" /></td>
<td><img src="image7.png" alt="Image 7" /></td>
<td><img src="image8.png" alt="Image 8" /></td>
</tr>
</tbody>
</table>
French-American-British (FAB) ALL classification

<table>
<thead>
<tr>
<th>Type</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL-L1</td>
<td>small uniform cells</td>
</tr>
<tr>
<td>ALL-L2</td>
<td>large varied cells</td>
</tr>
<tr>
<td>ALL-L3</td>
<td>large varied cells with vacuoles</td>
</tr>
</tbody>
</table>

Type of lymphocytes matters (B-cells or T-cells)
Classification

WBC amount in blood:

- leukemic (100-1000 $10^3/\mu L$)
- subleukemic (15-25 $10^3/\mu L$)
- leukopenic (<4 $10^3/\mu L$)
- aleukemic (normal amount; very rare)

(WBC normal amount is 4-9 $10^3/\mu L$)
## Clinical signs

<table>
<thead>
<tr>
<th>Acute</th>
<th>Chronic</th>
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<tr>
<td><strong>Abrupt onset</strong></td>
<td><strong>Gradual onset</strong></td>
</tr>
<tr>
<td><strong>Young adults and children</strong></td>
<td><strong>Adults and aged</strong></td>
</tr>
<tr>
<td><strong>Hiatus leukemicus (leukemic gap)</strong></td>
<td><strong>All forms are present, blasts are numerous</strong></td>
</tr>
<tr>
<td>- numerous blasts and a number of mature cells in the peripheral blood, with few or no intermediate forms</td>
<td></td>
</tr>
<tr>
<td><strong>Hemorrhagic syndrome, necroses and multiple ulcers in mucosae are typical</strong></td>
<td><strong>... only in blast crisis</strong></td>
</tr>
<tr>
<td></td>
<td>- chronic leukemia behaves like an acute, with rapid progression</td>
</tr>
<tr>
<td><strong>Liver, spleen and lymph nodes are slightly enlarged</strong></td>
<td><strong>... are considerably enlarged</strong></td>
</tr>
</tbody>
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# Pathology of acute leukemia

<table>
<thead>
<tr>
<th>AML</th>
<th>ALL</th>
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<tbody>
<tr>
<td>85% in adults</td>
<td>85% in children</td>
</tr>
<tr>
<td>“Pyoid” bone marrow (pus-like)</td>
<td>Crimson-red bone marrow</td>
</tr>
</tbody>
</table>

## Leukemic infiltration:

- bone marrow
- spleen
- liver
- lymph nodes
- GIT mucosae
- lungs
- pia mater - neuroleukemia (rare)

- lymph nodes
- spleen
- liver
- bone marrow
- thymus
- urinary tract
- pia mater (typical)
Features of neuroleukemia

- Leukemic infiltration of pia mater
- Leukemic infiltration leads to occlusion of CSF ways $\rightarrow$ intracranial hypertension
- Blast cells in CSF
Causes of death in acute leukemia

- Hemorrhages in vital organs
- Complications associated with necrotic and ulcerative processes in GIT (bleeding, perforation etc.)
- Secondary infection
- Suppression of bone marrow function
- Complications of therapy
## Chronic leukemias

<table>
<thead>
<tr>
<th>Myeloid</th>
<th>Lymphoid</th>
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<tbody>
<tr>
<td>chronic myeloid leukemia (CML)</td>
<td>chronic lymphocytic leukemia (CLL)</td>
</tr>
<tr>
<td>chronic erythroleukemia</td>
<td>lymphomatosis of skin (Sézary's disease)</td>
</tr>
<tr>
<td>erythremia</td>
<td>paraproteinemic leukemias</td>
</tr>
<tr>
<td>polycythemia vera (Vaquez-Osler disease)</td>
<td></td>
</tr>
</tbody>
</table>
# Pathology of chronic leukemia

<table>
<thead>
<tr>
<th>CML</th>
<th>CLL</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-40 years</td>
<td>40-60 years (never in children)</td>
</tr>
<tr>
<td>“Pyoid” bone marrow (pus-like)</td>
<td>Crimson-red bone marrow</td>
</tr>
<tr>
<td>Spleen enlargement</td>
<td>Lymph nodes enlargement</td>
</tr>
<tr>
<td>Philadelphia chromosome present</td>
<td>Philadelphia chromosome absent</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Leukemic infiltration:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Red pulp</td>
<td>Spleen</td>
</tr>
<tr>
<td>Sinusoids</td>
<td>Liver</td>
</tr>
<tr>
<td>Alveolar septs</td>
<td>Lungs</td>
</tr>
<tr>
<td>Leukemic “thrombi” in vessels → infarctions</td>
<td>Secondary infection, hemolytic anemia, thrombocytopenia</td>
</tr>
<tr>
<td>Blast crisis is typical</td>
<td>No blast crisis</td>
</tr>
</tbody>
</table>

- CML: Chronic Myeloid Leukemia
- CLL: Chronic Lymphoid Leukemia
Causes of death in chronic leukemia

- Secondary infection
- Organ dysfunction
- Compression of vital organs by enlarged lymph nodes
- Complications of therapy
Lymphoma

- Lymphoma is malignant neoplasm of lymphocytes or lymphoblasts that grow as nodular masses, usually in lymph nodes but sometimes in organs.
Main features of lymphomas

1. Lymph nodes enlargement
2. Common symptoms of intoxication (fever, profuse night sweat, weight loss)
3. Lymph nodes pathology:
   - loss of characteristic pattern
   - atypic cells
4. Can transform to leukemia (more than 25% of blast cells in bone marrow)
Aorta

Massively enlarged lymph nodes
Classification

- Hodgkin Lymphoma (HL)
- non-Hodgkin lymphomas (NHL)
Hodgkin lymphoma

- Age of patients:
  - 15–34 years
  - after 55 years

- Gradual involvement of lymph nodes: cervical, mediastinal, iliac, inguinal etc.

- Prominent tumor cell polymorphism

- Prognosis is more favorable than in NHL

- Characteristic spleen appearance (porphyry spleen)
Hodgkin lymphoma

- Cell types
  - Reed–Sternberg cell
  - Hodgkin cells: big and small
Hodgkin lymphoma

- Morphological types
  - Nodular sclerosing HL
  - Mixed-cellularity subtype
  - Lymphocyte-rich or Lymphocytic predominance
  - Lymphocyte depleted
Causes of death in Hodgkin lymphoma

- Compression of vital organs by enlarged lymph nodes
- Secondary infection
- Cachexia
- Amyloidosis
- Organ dysfunction
Non-Hodgkin lymphoma
# Features of lymphomas

<table>
<thead>
<tr>
<th>Non-Hodgkin</th>
<th>Hodgkin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simultaneous involvement of lymph nodes in different locations</td>
<td>Involvement of lymph nodes in one region (usually cervical) and then in others</td>
</tr>
<tr>
<td>Cell monomorphism</td>
<td>Cell polymorphism</td>
</tr>
<tr>
<td>Age of onset – usually after 40 years</td>
<td>Age of onset – children and young adults</td>
</tr>
<tr>
<td>Bad prognosis</td>
<td>Better prognosis (up to 80% of pediatric patients recover)</td>
</tr>
</tbody>
</table>
Classification of non-Hodgkin lymphomas

1. Cell size and morphology
2. Degree of maturity
3. Cytogenesis (T- and B- cells)
4. Involvement of lymph nodes
5. Degree of malignancy and prognosis:
   - low-intensity
   - aggressive
   - highly aggressive
**Burkitt's lymphoma (B-cell)**

- **Endemic variant** occurs in equatorial Africa. It is associated with Epstein-Barr virus (EBV) and translocations of gene MYC (located at 8q24). The disease involves the jaw or other facial bone, distal ileum, cecum, ovaries, kidney or the breast.

- **Sporadic variant** (a. k. a. "non-African") is another form of non-Hodgkin lymphoma found outside of Africa. It is associated with translocations of gene MYC and less with EBV.

- **Immunodeficiency-associated** Burkitt lymphoma is usually associated with HIV infection or occurs in the setting of post-transplant patients who are taking immunosuppressive drugs. Burkitt lymphoma can be one of the diseases associated with the initial manifestation of AIDS.
Pathology of Burkitt's lymphoma

- Areas of monomorphic cells with coarse chromatin and prominent nucleoli.
- The pattern of "Starry Sky" – histiocytes ("stars") against the dark lymphoma cells ("sky")
Burkitt's lymphoma
Paraproteinemic leukemias

- Multiple myeloma (Kahler's disease)
- Waldenström's macroglobulinemia
- Heavy chain disease (Franklin's disease and others)
Features of paraproteinemic leukemias

- Amyloidosis (AL-amyloidosis)
- Paraproteinemic edema (myocardium, kidney, lungs)
- Increased blood viscosity $\rightarrow$ paraproteinemic coma
Multiple myeloma

- Proliferation of atypical plasmocytes (myeloma cells) in bone marrow and other organs
- Myeloma cells produce paraproteins which are found in blood and urine (protein Bence Jones)
- Forms of growth: diffuse, diffuse nodular and multi-nodular
- Types: plasmocytic, plasmoblastic, polymorphonuclear cell, small cell myeloma
Multiple myeloma pathology

- Diffuse or focal myeloma infiltrates
- Localization of infiltrates:
  - flat bones (ribs, bones of the skull)
  - spine
  - long bones - rare
  - inner organs - the spleen, lymph nodes, liver, lungs, etc.
- Osteoporosis and osteolysis
- Myeloma nephropathy (myeloma contracted kidney) – main cause of death
Your diagnosis?