Lymphoma. Multiple myeloma.

Lymphogranulomatosis (Hodgkin's disease, Hodgkin's lymphoma).

Hodgkin's Lymphoma, lymphogranulomatosis (LGM) is tumor disease, initially localized in lymphoid tissue, substratum which is the giant multinuclear Reed–Sternberg cell.

**Etiology and pathogenesis:** According to modern ideas of the origin LGM a leading role is played by lymphotropic viruses (Epstein-Bar virus). Most current researchers follow the theory of primary focal origin of LGM.

**Classification:**
In ICD-10 coded following morphological variants of LGM (REAL-classification, 1994).
- C81.1 Nodular sclerosing HL
- C81.2 Mixed-cellularity subtype
- C81.3 Lymphocyte-rich or Lymphocytic predominance
- C81.0 Lymphocyte depleted
- C81.7 Unspecified

**Staging (Ann Arbor classification):**
- **Stage I**
  - I: Single Lymph Node region (I) or
  - IE: One extranodal site
- **Stage II**
  - II: Two or more lymph nodes on same side of diaphragm or
  - IIE: Local extralymphatic extension and one or more lymph nodes on same side diaphragm
- **Stage III**
  - III: Lymph nodes involve both sides diaphragm or
  - IIIE: Lymph nodes on both sides of diaphragm and localized Spleen or extralymphatic involved
- **Stage IV**
  - Diffuse or disseminated disease
  - Liver or Bone Marrow involvement

**Modifier**
- A: Asymptomatic
- B: Fever (>100 F), Night sweat, or weight loss (>10% in 6 months)

**An example of formulation of diagnosis:**
Lymphogranulomatosis, mixed-cell variant IIB, stage (with lesions of the cervical, mediastinal lymph nodes).

**Clinical features:**

**Patients with Hodgkin's lymphoma may present with the following symptoms:**

1. **Lymph nodes:** the most common symptom of Hodgkin's is the painless enlargement of one or more lymph nodes, or lymphadenopathy. The nodes may also feel rubbery and swollen when examined. The nodes of the neck and shoulders (cervical and supraclavicular) are most frequently involved (80–90% of the time, on average). The lymph nodes of the chest are often affected, and these may be noticed on a chest radiograph.
2. **Pain following alcohol consumption**: classically, involved nodes are painful after alcohol consumption, though this phenomenon is very uncommon, occurring in only two to three percent of people with Hodgkin's lymphoma, thus having a low sensitivity. On the other hand, its specificity is high enough for it to be regarded as a pathognomonic sign of Hodgkin lymphoma.

3. **Itchy skin**

4. **Night sweats**

5. **Unexplained weight loss**

6. **Splenomegaly**: enlargement of the spleen occurs in about 30% of people with Hodgkin's lymphoma. The enlargement, however, is seldom massive and the size of the spleen may fluctuate during the course of treatment.

7. **Hepatomegaly**: enlargement of the liver, due to liver involvement, is present in about 5% of cases.

8. **Hepatosplenomegaly**: the enlargement of both the liver and spleen caused by the same disease.

9. **Red-coloured patches on the skin**, easy bleeding and petechiae due to low platelet count (as a result of bone marrow infiltration, increased trapping in the spleen etc.—i.e. decreased production, increased removal)

10. **Systemic symptoms**: about one-third of patients with Hodgkin's disease may also present with systemic symptoms, including low-grade fever; night sweats; unexplained weight loss of at least 10% of the patient's total body mass in six months or less, itchy skin (pruritus) due to increased levels of eosinophils in the bloodstream; or fatigue (lassitude). Systemic symptoms such as fever, night sweats, and weight loss are known as B symptoms; thus, presence of fever, weight loss, and night sweats indicate that the patient's stage is, for example, 2B instead of 2A.

**Diagnostic criteria:**

1. Detection in biopsy of lymph node Reed–Sternberg cell.
2. Characteristic changes in the peripheral blood:
   - Neutrophilic leukocytosis with a shift to the left;
   - Relative or absolute lymphopenia (due to lesions of lymphoid tissue tumor process);
   - Eosinophilia, monocytosis;
   - Accelerated ESR.
3. In the myelogram - myeloid and mehakariocytic hyperplasia. In the IV stage lesions of bones can be detected Reed–Sternberg cell.

**The differential diagnosis:** Malignant lymphoma should be differentiated from reactive limfadenopatiy occurring in inflammatory processes, intoxication, after vaccination etc. Non-Hodgkin's malignant lymphoma.

**Treatment:** For the treatment used 3 options of therapy: radiation, polychemotherapy, combined treatment (radiation + PCT).

Current recommendations in accordance with the staging of the disease:

- Stage IA, IIA - subtotal lymph node irradiation;
- Stage IB IIB - combined therapy;
- Stage IIIA - PCT;
- Mediastinal tumor - combined therapy;
- Stage IIIB-IV - PCT.
**ABVD Regimen** (standard regimen) - Adriamycin (Doxorubicin), Bleomycin, Vinblastine, Dacarbazine.
**Stanford V** (experimental) - Adriamycin (Doxorubicin), Bleomycin, Vinblastine, Mechlorethamine, Vincristine, Etoposide, Prednisone.
**BEACOPP regimen** (experimental) - Adriamycin (Doxorubicin), Bleomycin, Vincristine, Procarbazine, Gemcitabine, Prednisone.
**MOPP regimen** (no longer used, listed for historical purposes) – Mechlorethamine, Vincristine, Procarbazine, Prednisone.

**Monoclonal Antibodies** (experimental)
- Anti-CD30 antibodies (SGN-30, MDX-060)
- Anti-CD20 antibodies (Rituximab)

**Prognosis**: Localized Hodgkin Lymphoma

**Adverse Factors**
- Mediastinal mass ratio >0.33 or >0.35
- Nodal mass >10 cm
- Age >50 years
- Nodal regions >2 or >3
- Increased Erythrocyte Sedimentation Rate
- B Symptoms of fever, Night Sweats and weight loss present

**Prognosis**: Advanced Hodgkin Lymphoma

Based on International Prognostic Factors for Advanced Hodgkin Lymphoma
- Risk Factors
- Stage IV Disease
- Male gender
- Age 45 years or older
- Hemoglobin <10.5 g/dl
- White Blood Cell count >15,000/ul
- Lymphocyte Count <600/ul
- Albumin <4g/dl

**Overall survival rates after treatment**
- Post-treatment by 1 year: 94% survival rate
- Post-treatment by 5 years: 85% survival rate
- Post-treatment by 10 years: 82% survival rate
- Post-treatment by 15 years: 74% survival rate
- Post-treatment by 20 years: 63% survival rate

**Five years survival rates based on staging (see above)**
- Stage I: 90-95%
- Stage 2: 90-95%
- Stage 3: 85-90%
- Stage 4: 80%
Non-Hodgkin's Lymphoma

Definition: Hemoblastosis of lymphoid cells outside the bone marrow. This tumor clone can have both B - (80-85%) and T-cell nature (about 15%).

According REAL classification distinguish 10 forms of B-cell and 10 forms of T-cell origin. These forms are distinguished by cell maturity. Highly differentiated lymphocytic lymphoma (lymphoma of the small lymphocytes by REAL classification retain cytomorphological features and immunophenotype characteristic to B-lymphocytes. Lymphoblastic lymphoma high degree of malignancy of B and T cells are monomorphic cellular composition and differ only by the expression of antigens, some cytochemical and cytogenetic characteristics.

By the nature of growth divided into two versions:
- Nodular (follicular) - For the nodular lymphomas is typical the formation of pseudo follicular structures, unlike of the true follicles are not only in cortical, but in the cerebral layer of lymph nodes, are large, fuzzy contours. Follicular growth inherent mainly B-lymphocytes from follicular-center
- Diffuse forms - Diffuse type of growth with total growth of cells, complete erasure of lymph node structures typical of all types.

Example of formulation of diagnosis:
NHL, follicular, mainly of small cells with split core, low degree of malignancy, stage IIIb.
NHL, diffuse B-limfoblastic, high degree of malignancy with leukemization (IV B stage).

Clinical features:
The most common primary localization of process is peripheral lymph nodes (60% of patients). Primary abdominal lymph node lesions is observed in about 20% Mediastinal - 9% extranodal localization - in 8% of patients. Presence of Lymphadenopathy draining Waldeyer's ring, epitrochlear lymph nodes, mediastinal, abdominal and extranodal involvement, chest Pain (suggests lung involvement), systemic symptoms more common in Hodgkin's. The main clinical feature is splenomegaly. For a long time is asymptomatic disease.

Diagnostic criteria:
1. Non-Hodgkin's Lymphoma can be diagnosed only by studying the histological structure of lymph node or biopsy of extra-nodular tissue.
2. Refinement of the morphology of tumor cells possibly by examining of aspirate cytology and prints of lymph nodes.

Treatment:
Combination Chemotherapy and Radiation Therapy
Scheme CHOP (cyclophosphamide, doxorubicin, onkoin (vincristine), prednisone) - the "gold standard" of therapy
Monoclonal Antibody in certain cases - Rituxan binds antigen on mature B Cells

Prognosis:
I. Sluggish, chronic course - (lifetime 5 years):
- Lymphoma of the small lymphocytes (prolimfocytic);
- Marginal zone lymphoma of the spleen;
- Follicular lymphoma, extranodular lymphoma associated with mucous membranes;
- Fungal mycosis.

II. Aggressive course (lifetime up to 1 year):
- Diffuse B - large cell lymphoma;
- Aplastic large cell lymphoma.

III. Highly aggressive (acute) course (duration less than 1 year):
- B-lymphoblastic lymphoma;
- T-lymphoblastic lymphoma;
- Burkitt's lymphoma

**Adverse prognostic factors:**
1. Engaging in the pathological process of bone marrow - leukemization.
2. The presence of more than one extra nodular focus.
3. The presence of intoxication.
4. Advanced age.
5. The male sex

**Multiple myeloma**

Multiple myeloma is clonal malignant disease caused by proliferation in the bone marrow plasmatic cells secreting structurally homogeneous immunoglobulins. It is tumor like lesions of bone marrow (diffuse, diffuse-focal, at least - focal) with the development of bone destructive changes (osteoporosis, osteolysis) and monoclonal immunoglobulin syndrome (paraproteinemia).

**Classification:** According to clinical and anatomic classification (NE Andreev, 1998, 2003) are the following forms of MM:
- Diffusely - focal (60% of patients);
- Diffuse (24% patients);
- Multiple-focal (15% of patients);
- Rare form (sclerosing, mainly visceral (1%).

**Clinical stage:**

<table>
<thead>
<tr>
<th>Stages</th>
<th>Criteria</th>
<th>Tumor weight (kg/m²)</th>
<th>Subclasses</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>The combination of features 1-4</td>
<td>To 0.6 (low)</td>
<td>A. creatinine &lt;0.02 g / l</td>
</tr>
<tr>
<td></td>
<td>1. Hb&gt; 100 g / l.</td>
<td></td>
<td>B. creatinine &gt; 0.02 g / l</td>
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<td>2. Ca ++ serum to 2.6 mmol / l.</td>
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<td></td>
<td>3. Lack of osteolytic bone lesions or 1solitary.</td>
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<tr>
<td></td>
<td>4. IgG &lt;50 g / l, IgA &lt;30 g / l protein BG in the urine &lt;4 g / day.</td>
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</tbody>
</table>

Table 1.
Indicators intermediate between stages I and III

<table>
<thead>
<tr>
<th>III</th>
<th>One of the following characteristics:</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>1. Hb &lt; 85 g / l.</td>
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<td>2. Serum Ca ++&gt; 2.6 mmol / l.</td>
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<td></td>
<td>3. Osteo - destructive process</td>
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<td>4. High level of M-component: IgG&gt; 70 g / l,</td>
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<tr>
<td></td>
<td>IgA&gt; 50 g / l protein BG in the urine &gt; 12 g / day.</td>
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More than 1.2 (high)

In the course of the disease are two phases:
1. Chronic (expanded).
2. Acute (terminal).

**Example formulation of a diagnosis:** Multiple myeloma, diffusely - focal form, II a stage, chronic phase.

**Clinical picture:** Clinical symptoms of MM presented in Table. 2

### The main syndromes and complications of multiple myeloma

<table>
<thead>
<tr>
<th>Syndromes</th>
<th>Pathogenesis, clinical manifestations, complications.</th>
</tr>
</thead>
<tbody>
<tr>
<td>The affect of the bones (80%)</td>
<td>Osteo - destruction flat bones (spine, ribs, skull, etc.), osalgia 70%, pathologic compression fractures (vertebral compression). Radiological findings: osteolytic defects rounded shape without marginal sclerosis. Diffuse osteoporosis, rarely - osteosclerosis.</td>
</tr>
<tr>
<td>The affect of the nervous system</td>
<td>The result of bone damage - dissemination of process at the spinal cord or nerve roots as a result of hypercalcemia, increased blood viscosity. 30% - compression of the spinal cord, radiculopathy, paraplegia, encephalopathy, mental disorders.</td>
</tr>
<tr>
<td>Myeloma nephropathy (50%).</td>
<td>Excretion of paraprotein - tubular lesions, paraamyloidosis, hypercalcemia, hyperuricemia, increased blood viscosity (violation of glomerular filtration, acute and chronic renal insufficiency without edema and hypertension, proteinuria Bence-Jones.</td>
</tr>
</tbody>
</table>
| Hyperviscose syndrome (10-25%) | Myeloma proteins (M-protein) cause albuminosi, aggregate and polymerized, breaking microcirculation (s. Reynaud, gangrene of the distal limbs, blurred vision, retinopathy, paraproteyinemic coma. In the presence of cryo globulin symptoms grow after the cooling - the result of hyperviscose syndrome, M-proteins absorbed on platelets, form a
<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhagic syndrome (15%)</td>
<td>Because of Hyper viscose syndrome, M-proteins absorbed on platelets, form a complexes with coagulation factors: V, VII, VIII, II, I.</td>
</tr>
<tr>
<td>Hipercalcemia (10-20%)</td>
<td>From 2.6 to 3.5 mmol / l - average severity, more than 3.5 mmol / l - severe toxic. Myeloma cells synthesize factor activating osteoclasts. Clinic: nausea, vomiting, constipation, thirst, polyuria, loss of orientation, psychosis, sopor, coma.</td>
</tr>
<tr>
<td>Violation of haematopoiesis</td>
<td>Local suppression of bone marrow tumor nodes and / or multiple myeloma infiltration leads to anemia, neutropenia. In a blood test - acceleration of ESR, erythrocyte clumping in the form of coin columns. In the bone marrow - plazmocytosis (10-30%).</td>
</tr>
<tr>
<td>Outside bone marrow proliferation.</td>
<td>Splenomegaly (15-30%), hepatomegaly (17-26%), rarely - lymphadenopathy, changes in the lung, thyroid, gastrointestinal tract, pericardium.</td>
</tr>
<tr>
<td>Immunological failure</td>
<td>Inhibition of normal immunoglobulin synthesis, hypogammaglobulinemia, recurrent urinary infections and respiratory tract infections (bacterial and due to the herpes virus).</td>
</tr>
<tr>
<td>Paraamyloidosis</td>
<td>Affected blood vessels, muscles, skin, joints and tendons. Clinic - increasing heart failure, macroglossia, chronic renal failure and others.</td>
</tr>
</tbody>
</table>

**Course:** Distinguish the (N.E Andreeva, 2003):
- "Smoldering MM" no signs of progression for many months (years);
- Slowly progressive (indolent) form: remission 5 years or more;
- Active - in response to first line therapy; quickly progressing - "aggressive", with primary or secondary resistance to chemotherapy.

**Diagnostic criteria:**
Diagnosis of MM is based on two criteria:
1. Plasma cell infiltration of the bone marrow (plasmocytes in punctate > 10%).
2. Monoclonal imunohlobulinopathy (serum M-component or Bence-Jones protein in the urine of more than 50 mg / l).

Before the treatment patients should conduct the next minimum amount of research to determine the form of MM.
1. General blood test with calculation of reticulocytes, platelets, time coagulation, tests Duke.
2. General analysis of urine (protein BG).
3. Sternal puncture (myelogram).
4. Determination of total protein serum, protein electrophoresis to determine the presence and content of M-component.
5. Determination of serum creatinine, calcium, sodium, potassium.
6. X-ray bones.
7. Investigation of C-reactive protein and serum β2-microglobulin.
8. Analysis of urine Zimnitskiy

In accordance with current requirements availability of MM must be confirmed by immunophenotyping results.

**Treatment:**
Chemotherapy
The use of α-interferon
The use of bisphosphonates
Symptomatic therapy

**Prognosis. Factors high risk includes:**
1. The percentage of bone marrow plasmocytosis more than 30% - aggressive MM.
2. The morphological variant of the disease: mature - indolent, the presence of immature forms – active, plasmablastic - aggressive MM.
3. Rapid tumor growth with the increase of bone destruction.
5. The level of β2 MG more than 6 mg / l.
6. High levels of CRP (interleukin-6) IL-6 causes an increase in C-reactive protein, so the level of this protein can be considered as a marker of IL-6 (IL-6 is able to enhance the production of immature myeloma cells activate osteoblasts).
7. The level of serum calcium above 3.5 mmol / l.
8. Violation of karyotype (in I stage MM detected in 20%, in the third - 60% of patients).
9. The rapid increase of serum paraprotein, BG protein in the urine.
10. Advanced age, presence of soft tissue metastases.