

**MINISTRY OF HEALTHCARE OF UKRAINE
HSEEU "Ukrainian Medical Stomatological Academy"**

"Approved"

at the meeting of internal
medicine №1 department

Head of Department

Prof. Skrypnyk I.M.

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**GUIDELINES
FOR STUDENTS
INDEPENDENT WORK
IN THE PRACTICAL CLASSES PREPARING**

<i>Academic discipline</i>	Internal medicine
<i>Module</i>	Current practice of internal medicine
<i>Content module</i>	Management of the patients with main symptoms and syndromes in hematology clinic
<i>Study subject</i>	Management of the patients with lymphadenopathy
<i>Course</i>	VI
<i>Faculty</i>	of foreign students training

Poltava 2016.

The subject of the lesson: Lymphadenopathies

Lymph nodes, in conjunction with the spleen, tonsils, adenoids, and Peyer patches, are highly organized centers of immune cells that filter antigen from the extracellular fluid. Directly interior to the fibrous capsule is the subcapsular sinus. This allows lymph, an ultrafiltrate of blood, to traverse from the afferent lymph vessels, through the sinuses, and out the efferent vessels. The sinuses are studded with macrophages, which remove 99% of all delivered antigens.

Interior to the subcapsular sinus is the cortex, which contains primary follicles, secondary follicles, and the interfollicular zone. Follicles within the cortex are major sites of B-cell proliferation, whereas the interfollicular zone is the site of antigen-dependent T-cell differentiation and proliferation. The deepest structure within the lymph node is the medulla, consisting of cords of plasma cells and small B lymphocytes that facilitate immunoglobulin secretion into the exiting lymph.

The lymph node, with its high concentration of lymphocytes and antigen-presenting cells, is an ideal organ for receiving antigens that gain access through the skin or gastrointestinal tract. Nodes have considerable capacity for growth and change. Lymph node size depends on the person's age, the location of the lymph node in the body, and antecedent immunological events. In neonates, lymph nodes are barely perceptible, but a progressive increase in total lymph node mass is observed until later childhood. Lymph node atrophy begins during adolescence and continues through later life.

Lymphadenopathy reflects disease involving the reticuloendothelial system, secondary to an increase in normal lymphocytes and macrophages in response to an antigen. Most lymphadenopathy in children is due to benign self-limited disease such as viral infections. Other less common etiologies responsible for adenopathy include nodal accumulation of inflammatory cells in response to an infection in the node (lymphadenitis), neoplastic lymphocytes or macrophages (lymphoma), or metabolite-laden macrophages in storage diseases (Gaucher disease).

The aims of the training course:

To know:

- etiology and pathogenesis of lymphadenopathy.
- classification of lymphadenopathy.
- the basic clinical syndromes lymphadenopathy.
- differential diagnosis lymphadenopathy.
- main principles of treatment lymphadenopathy.

To be able:

- to take anamnesis from a patients
- to survey the patient, to reveal and to give the estimation to the changes of the patient's condition
- to draw up a plan of additional investigations to estimate their results
- to prescribe proper treatment

Contents of the training materials Generalized lymphadenopathy is defined as enlargement of more than 2 noncontiguous lymph node groups. A thorough history and physical examination are critical in establishing a diagnosis. Causes of generalized lymphadenopathy include infections, autoimmune diseases, malignancies, histiocytoses, storage diseases, benign hyperplasia, and drug reactions.

- Infections
 - Generalized lymphadenopathy is most often associated with systemic viral infections.
 - Infectious mononucleosis results in widespread adenopathy.
 - Roseola infantum (caused by human herpes virus 6), cytomegalovirus (CMV), varicella, and adenovirus all cause generalized lymphadenopathy.

- Human immunodeficiency virus (HIV) is often associated with generalized adenopathy, which may be the presenting sign. Children with HIV are at increased risk for tuberculosis, as well.
- Although usually associated with localized node enlargement, some bacterial infections present with generalized adenopathy. Examples include typhoid fever caused by *Salmonella typhi*, syphilis, plague, and tuberculosis. Less common bacteremias, including those caused by endocarditis, result in generalized lymphadenopathies.
- Malignant etiologies
 - Concern about malignant etiologies often drives further diagnostic testing in children with adenopathy. Malignancy is often associated with constitutional signs, such as fever, anorexia, nonspecific aches and pains, weight loss, and night sweats. The acute leukemias and lymphomas often present with these nonspecific findings.
 - Generalized lymphadenopathy is present at diagnosis in two thirds of children with acute lymphoblastic leukemia (ALL) and in one third of children with acute myeloblastic leukemia (AML). Abnormalities of peripheral blood counts usually lead to the correct diagnosis. The lymphomas more often present with regional lymphadenopathy, but generalized lymphadenopathy occurs.
 - Constitutional signs and symptoms observed in the leukemias are less reliable findings in the lymphomas. Only one third of children with Hodgkin disease and 10% with non-Hodgkin lymphoma display them. Malignancies usually present with nodes that tend to be firmer and less mobile or matted; however, this finding can be misleading. Benign reactive lymph nodes may be associated with fibrotic reactions that make them firm.
- Storage diseases: Generalized lymphadenopathy is an important manifestation of the lipid storage diseases. In Niemann-Pick disease, sphingomyelin and other lipids accumulate in the spleen, liver, lymph nodes, and CNS. In Gaucher disease, the accumulation of the glucosylceramide leads to the engorgement of the spleen, lymph nodes, and the bone marrow. Although widespread lymphadenopathy is common, additional findings, such as hepatosplenomegaly and developmental delay in Niemann-Pick disease and blood dyscrasias in Gaucher disease, are usually present. These diagnoses are established by leukocyte assay.
- Drug reactions: Adverse drug reactions can cause generalized lymphadenopathy. Within a couple of weeks of initiating phenytoin, some patients experience a syndrome of regional or generalized lymph node enlargement, followed by a severe maculopapular rash, fever, hepatosplenomegaly, jaundice, and anemia. These symptoms abate 2-3 months after discontinuation of the drug. Several other drugs are implicated in similar symptomatology, including mephenytoin, pyrimethamine, phenylbutazone, allopurinol, and isoniazid.
- Other nonneoplastic etiologies: Rare nonneoplastic causes of generalized lymphadenopathy include Langerhans cell histiocytosis and Epstein-Barr virus (EBV)-associated lymphoproliferative disease. Autoimmune etiologies include juvenile rheumatoid arthritis, which often presents with adenopathy, especially during the acute phases of the disease. Sarcoidosis and graft versus host disease also merit consideration.

Regional lymphadenopathy involves enlargement of a single node or multiple contiguous nodal regions. Lymph nodes are clustered in groups throughout the body and are concentrated in the head and neck, axillae, mediastinum, abdomen, and along the vascular trunks of the extremities. Each group drains lymph from a particular region of the body. Knowledge of the pattern of lymph drainage aids in determining the etiology.

- Cervical lymphadenopathy: Cervical lymphadenopathy is a common problem in children. Cervical nodes drain the tongue, external ear, parotid gland, and deeper structures of the neck, including the larynx, thyroid, and trachea. Inflammation or direct infection of these areas causes subsequent engorgement and hyperplasia of their respective node groups. Adenopathy is most common in cervical nodes in children and is usually related to infectious etiologies. Lymphadenopathy posterior to the sternocleidomastoid is typically a more ominous finding, with a higher risk of serious underlying disease.

- Infectious etiologies
 - Cervical adenopathy is a common feature of many viral infections. Infectious mononucleosis often manifests with posterior and anterior cervical adenopathy. Firm tender nodes that are not warm or erythematous characterize this lymph node enlargement. Other viral causes of cervical lymphadenopathy include adenovirus, herpesvirus, coxsackievirus, and CMV. In herpes gingivostomatitis, impressive submandibular and submental adenopathy reflects the amount of oral involvement.
 - Bacterial infections cause cervical adenopathy by causing the draining nodes to respond to local infection or by the infection localizing within the node itself as a lymphadenitis. Bacterial infection often results in enlarged lymph nodes that are warm, erythematous, and tender. Localized cervical lymphadenitis typically begins as enlarged, tender, and then fluctuant nodes. The appropriate management of a suppurative lymph node includes both antibiotics and incision and drainage. Antibiotic therapy should always include coverage for *Staphylococcus aureus* and *Streptococcus pyogenes*.
 - In patients with cervical adenopathy, determine whether the patient has had recent or ongoing sore throat or ear pain. Examine the oropharynx, paying special attention to the posterior pharynx and the dentition. The classic manifestation of group A streptococcal pharyngitis is sore throat, fever, and anterior cervical lymphadenopathy. Other streptococcal infections causing cervical adenopathy include otitis media, impetigo, and cellulitis.
 - Atypical mycobacteria cause subacute cervical lymphadenitis, with nodes that are large and indurated but not tender. The only definitive cure is removal of the infected node. ^[12]
 - Mycobacterium tuberculosis may manifest with a suppurative lymph node identical to that of atypical mycobacterium. Intradermal skin testing may be equivocal. A biopsy may be necessary to establish the diagnosis.
 - Catscratch disease, caused by *Bartonella henselae*, presents with subacute lymphadenopathy often in the cervical region. The disease develops after the infected pet (usually a kitten) inoculates the host, usually through a scratch. Approximately 30 days later, fever, headache, and malaise develop, along with adenopathy that is often tender. Several lymph node chains may be involved. Suppurative adenopathy occurs in 10-35% of patients. Antibiotic therapy has not been shown to shorten the course.
- Noninfectious etiologies
 - Malignant childhood tumors develop in the head and neck region in one quarter of cases. In the first 6 years of life, neuroblastoma, leukemia, non-Hodgkin lymphoma, and rhabdomyosarcoma (in order of decreasing frequency) are most common in the head and neck region. In children older than 6 years, Hodgkin disease and non-Hodgkin lymphoma both predominate. Children with Hodgkin disease present with cervical adenopathy in 80-90% of cases as opposed to 40% of those with non-Hodgkin lymphoma.
 - Kawasaki disease is an important cause of cervical adenopathy. These children have fever for at least 5 days, and cervical lymphadenopathy is one of the 5 diagnostic criteria (of which 4 are necessary to establish the diagnosis).
- Submaxillary and submental lymphadenopathy: These nodes drain the teeth, tongue, gums, and buccal mucosa. Their enlargement is usually the result of localized infection, such as pharyngitis, herpetic gingivostomatitis, and dental abscess.
- Occipital lymphadenopathy: Occipital nodes drain the posterior scalp. These nodes are palpable in 5% of healthy children. Common etiologies of occipital lymphadenopathy include tinea capitis, seborrheic dermatitis, insect bites, orbital cellulitis, and pediculosis. Viral etiologies include rubella and roseola infantum. Rarely, occipital lymphadenopathy may be noted after enucleation of the eye for retinoblastoma.
- Preauricular lymphadenopathy: Preauricular nodes drain the conjunctivae, skin of the cheek, eyelids, and temporal region of the scalp and rarely are palpable in healthy children. The oculoglandular syndrome consists of severe conjunctivitis, corneal ulceration, eyelid edema, and

ipsilateral preauricular lymphadenopathy. Chlamydia trachomatis and adenovirus can cause this syndrome.

- Mediastinal lymphadenopathy
 - Mediastinal nodes drain the thoracic viscera, including the lungs, heart, thymus, and thoracic esophagus. Because these nodes are not directly demonstrable upon physical examination, their enlargement must be indirectly assessed. Supraclavicular adenopathy is often associated with mediastinal adenopathy. Mediastinal nodes may cause cough, wheezing, dysphagia, airway erosion with hemoptysis, atelectasis, and the obstruction of the great vessels, which constitutes superior vena cava syndrome. Airway compromise may be life threatening.
 - Mediastinal lymphadenopathy is usually a sign of serious underlying disease. More than 95% of mediastinal masses are caused by tumors or cysts. Lymphomas and acute lymphoblastic leukemia are the most common etiologies and usually involve the anterior mediastinum. These malignancies are associated with a high risk of superior vena cava syndrome and are associated with several potentially life-threatening complications, as follows:
 - The danger of sedation of patients, especially in the supine position for scans and procedures (The prone position actually may be safer.)
 - The risk during intubation of these patients, usually at the time of biopsy or placement of a central venous catheter
 - The risk of cardiovascular collapse during general anesthesia because of compression of venous return or because of previously undiagnosed pleural effusions
 - The risk of losing the ability to establish a pathologic diagnosis because of the use of steroids or radiation therapy
 - Unlike most other adenopathies, mediastinal lymphadenopathy is less frequently a result of infection. Infections frequently involve the hilar region and include histoplasmosis, coccidioidomycosis, and tuberculosis.
 - Nonlymphoid mediastinal tumors may be confused with adenopathy. These include neurogenic tumors (usually found in the posterior mediastinum), germ cell tumors, and teratomas.
 - Nonneoplastic conditions may also be confused with mediastinal adenopathy. These include the typically large thymus of a child, substernal thyroid glands, bronchogenic cysts, and abnormalities of the great vessels.
- Supraclavicular lymphadenopathy
 - Supraclavicular nodes drain the head, neck, arms, superficial thorax, lungs, mediastinum, and abdomen. Left supraclavicular nodes also reflect intra-abdominal drainage and enlarge in response to malignancies in that region. This is particularly true when adenopathy in this region occurs in the absence of other cervical adenopathy.
 - Right supraclavicular nodes drain the lung and mediastinum and are typically enlarged with intrathoracic lesions.
 - Serious underlying disease is frequent in children with supraclavicular adenopathy and always merits further evaluation. The potential for malignancy necessitates peripheral blood counts, skin testing for tuberculosis, and chemical studies, including uric acid, lactate dehydrogenase, calcium (Ca), phosphorus (P), and renal and hepatic function studies. Chest radiography and possibly CT scanning are indicated.
 - Several important infections may occur with supraclavicular adenopathy, including tuberculosis, histoplasmosis, and coccidioidomycosis.
 - Early lymph node biopsy should be considered in children with supraclavicular adenopathy.
- Axillary lymphadenopathy
 - Axillary nodes drain the hand, arm, lateral chest, abdominal walls, and the lateral portion of the breast.
 - A common cause of axillary lymphadenopathy is catscratch disease. Local axillary skin infection and irritation commonly are associated with local adenopathy. Other etiologies include

recent immunizations in the arm (particularly with bacille Calmette-Guerin vaccine), brucellosis, juvenile rheumatoid arthritis, and non-Hodgkin lymphoma.

- Hidradenitis suppurativa is a condition of enlarged tender lymph nodes that typically affects children with obesity and is caused by recurrent abscesses of lymph nodes in the axillary chain. The etiology is unknown, and treatment may include antibiotics. Many patients require incision and drainage.

- Abdominal lymphadenopathy

- Abdominal nodes drain the lower extremities, pelvis, and abdominal organs. Although abdominal adenopathy is not usually demonstrable upon physical examination, abdominal pain, backache, increased urinary frequency, constipation, and intestinal obstruction secondary to intussusception are possible presentations.

- Mesenteric adenitis is thought to be viral in etiology and is characterized by right lower quadrant abdominal pain caused by nodal enlargement near the ileocecal valve. Differentiating mesenteric adenitis from appendicitis may be difficult.

- Mesenteric adenopathy may be caused by non-Hodgkin lymphoma or Hodgkin disease.

- Typhoid fever and ulcerative colitis are other etiologies of mesenteric adenopathy.

- Iliac and inguinal lymphadenopathy: The lower extremities, perineum, buttocks, genitalia, and lower abdominal wall drain to these nodes. They are typically palpable in healthy children, although they are usually no larger than 1-1.5 cm in diameter. Regional lymphadenopathy is typically caused by infection; however, insect bites and diaper dermatitis are also frequent. Nonlymphoid masses that may be confused with adenopathy include hernias, ectopic testes, and lipomas.

Outline - Etiologies of Lymphadenopathy

I. Generalized lymphadenopathy

1. Infections

1. Viral

- Common upper respiratory infections
- Infectious mononucleosis
- CMV
- Hepatitis A, B, and C
- Acquired immunodeficiency syndrome
- Rubella
- Varicella
- Measles

2. Bacterial

- Septicemia
- Typhoid fever
- Tuberculosis
- Syphilis
- Plague

3. Protozoal - Toxoplasmosis

4. Fungal - Coccidioidomycosis

2. Autoimmune disorders and hypersensitivity states

1. Juvenile rheumatoid arthritis
2. Systemic lupus erythematosus
3. Drug reactions (eg, phenytoin, allopurinol)
4. Serum sickness

3. Storage Diseases

1. Gaucher disease
2. Niemann-Pick disease

4. Neoplastic and proliferative disorders

1. Acute leukemias

2. Lymphomas (Hodgkin, non-Hodgkin)
3. Neuroblastoma
4. Histiocytoses

II. Regional lymphadenopathy

1. Cervical
 1. Viral upper respiratory infection
 2. Infectious mononucleosis
 3. Rubella
 4. Cat scratch disease
 5. Streptococcal pharyngitis
 6. Acute bacterial lymphadenitis
 7. Toxoplasmosis
 8. Tuberculosis/atypical mycobacterial infection
 9. Acute leukemia
 10. Lymphoma
 11. Neuroblastoma
 12. Rhabdomyosarcoma
 13. Kawasaki disease
2. Submaxillary and submental
 1. Oral and dental infections
 2. Acute lymphadenitis
3. Occipital
 1. Pediculosis capitis
 2. Tinea capitis
 3. Secondary to local skin infection
 4. Rubella
 5. Roseola
4. Preauricular
 1. Local skin infection
 2. Chronic ophthalmic infection
 3. Cat scratch disease
5. Mediastinal
 1. Acute lymphoblastic leukemia
 2. Lymphoma
 3. Sarcoidosis
 4. Cystic fibrosis
 5. Tuberculosis
 6. Histoplasmosis
 7. Coccidioidomycosis
6. Supraclavicular
 1. Lymphoma
 2. Tuberculosis
 3. Histoplasmosis
 4. Coccidioidomycosis
7. Axillary
 1. Local infection
 2. Cat scratch disease
 3. Brucellosis
 4. Reactions to immunizations
 5. Lymphoma
 6. Juvenile rheumatoid arthritis
8. Abdominal

1. Acute mesenteric adenitis
2. Lymphoma
9. Inguinal
 1. Local infection
 2. Diaper dermatitis
 3. Insect bites
 4. Syphilis
 5. Lymphogranuloma venereum

NHLs

NHLs are a heterogeneous group of lymphoproliferative malignancies with varying morphologic features depending on the specific type of this disorder. The abnormal lymphocytes in the lymph node, bone marrow, or extranodal sites can be small cleaved or noncleaved, intermediate, or large cell and can have a follicular or diffuse pattern. In contrast with reactive follicular hyperplasia, lymphomas usually alter the lymph node architecture, and the capsule is usually involved.

Staging. Staging is important in selecting a treatment and also for prognosis. CT scans of the neck, chest, abdomen, and pelvis, as well as bilateral bone marrow aspirate and biopsy, are necessary to stage the lymphoma. Noncontiguous lymph node involvement, uncommon in Hodgkin disease, is more common among patients with NHL.

The Ann Arbor staging system is the most commonly used staging system for patients with NHL.

Stage I NHL involves a single lymph node region (I) or localized involvement of a single extralymphatic organ or site (IE).

Stage II NHL involves 2 or more lymph node regions on the same side of the diaphragm (II) or localized involvement of a single associated extralymphatic organ in addition to criteria for stage II (IIE).

Stage III involves lymph node regions on both sides of the diaphragm (III) that also may be accompanied by localized involvement of an extralymphatic organ or site (IIIE), spleen (IIIS), or both (IIISE).

Stage IV represents disseminated or multifocal involvement of one or more extralymphatic sites with or without associated lymph node involvement or isolated extralymphatic organ involvement with distant (nonregional) nodal involvement.

Subscript letters designate involvement of extralymphatic organs, as follows: L, lung; H, liver; P, pleura; O, bone; M, bone marrow; and D, skin. The designation E is used when extranodal lymphoid malignancies arise in tissues that are separate from but near the major lymphatic aggregates.

In this system, stages I-IV can be appended by A or B designations. Patients with A disease do not have systemic symptoms. The B designation is applied in patients with any of the following symptoms: unexplained loss of more than 10% of body weight in the preceding 6 months before diagnosis, unexplained fever with temperature above 38°C, and drenching night sweats.

In addition to staging, risk stratification is important in patients with NHL. Several scoring systems had been developed and validated prospectively in patients with diffuse large B-cell lymphoma (International Prognostic Index, IPI) or follicular B-cell lymphomas (Follicular Lymphoma International Prognostic Index, FLIPI) that can be used to predict the prognosis of patients with B-cell malignancies.

General treatment information

Once non-Hodgkin lymphoma has been diagnosed and staged, your cancer care team will discuss treatment options with you. Several different types of treatment can be used against non-Hodgkin lymphoma. The treatment options depend on the type of lymphoma and its stage (extent), as well as the other prognostic factors. Of course, no 2 patients are exactly alike, and standard options are often tailored to each patient's situation.

The main types of treatment for non-Hodgkin lymphoma are:

- Chemotherapy

- Immunotherapy
- Targeted therapy
- Radiation
- Stem cell transplant

In rare cases, surgery is also used.

Chemotherapy regimens:

R-CHOP	Days 1, 22, and 43: Rituximab 375mg/m ² IV 7 days prior to beginning CHOP regimen Day 1: Cyclophosphamide 750mg/m ² IV + doxorubicin 50mg/m ² IV bolus + vincristine 1.4mg/m ² IV bolus (max dose 2mg) Days 3, 24, and 45: Prednisone 100mg orally 5 days. Repeat each cycle every 3 weeks for 3 cycles. Radiotherapy begins 3 weeks after last cycle of R-CHOP.
Bendamustine ± rituximab	Days 1–2: Bendamustine 120mg/m ² IV, ± Day 1: Rituximab 375mg/m ² IV. Repeat every 28 days for up to 6 cycles.
Lenalidomide ± rituximab (non-GCB DLBCL) ⁴²⁻⁴⁴	Days 1–21: Lenalidomide 20mg orally ± rituximab 375mg/m ² IV weekly during cycle 1. Repeat every 28 days until complete response.
Patients >80 Years of Age With Comorbidities	
R-mini-CHOP ¹⁶	Day 1: Rituximab 375mg/m ² IV Day 1: Cyclophosphamide 400mg/m ² IV + doxorubicin 25mg/m ² IV + vincristine 1mg IV Days 1–5: Prednisone 40mg/m ² orally. Repeat every 3 weeks for 6 cycles.
Consolidation (optional)	
High-dose therapy with autologous stem cell rescue in patients with age-adjusted IPI high-risk disease (Category 2B)	Induced with 5 cycles of CHOP or R-CHOP <u>followed by</u> autotransplantation at the first response to induction therapy with CHOP with or without rituximab for 3 cycles.
High-dose therapy with autologous stem cell rescue in patients with double-hit DLBCL	Induced with 5 cycles of CHOP or R-CHOP followed by autotransplantation at the first response to induction therapy with CHOP with or without rituximab for 3 cycles.

Chronic lymphoid leukemia (CLL; chronic lymphocytic leukemia) (ICD-10 C 91.1) – the malignant hematopoiesis disorder, which substrate is small morphologically mature lymphoid elements originating from B-and T-lymphocytes, they proliferate and accumulate in the peripheral blood, bone marrow and lymphoid tissue.

Etiology. A clear dependence of the CLL incidence from the mutagenic factors effect (ionizing radiation, chemicals) has not been identified. An increased frequency in families of patients with chronic lymphoproliferative diseases is proven, high hereditary risk of late penetration. Sometimes CLL registered in 3-4 generations with the phenomenon of anticipation – reducing age of the disease debut in each subsequent generation.

Pathogenesis. CLL is a clonal disease, that is a result of neoplastic transformation, when the cell life expectancy increasing and the inhibition of apoptosis (programmed cell death), with the uncontrolled B-lymphocytes proliferation and gradual replacement of normal hematopoiesis, leading to the development of anemia, thrombocytopenia. Initial genetic disorders occur in immature B-

lymphocytes, which is confirmed by the fact they express cluster of differentiation – CD5+, which is associated with autoimmune phenomena.

Pathogenetically for "mutation status" there are two types of CLL with different clinical course, sensitivity to therapy and, consequently, prognosis:

1 mutated CLL «m-CLL» – the tumor substrate are in lymphocytes exposed to antigen (memory cells). Mutations variable region genes (Vh genes) of B-lymphocytes arise in the secondary follicle lymph nodes, aimed at increasing the affinity of antibodies to antigens.

2. unmutated CLL «u-CLL» – tumor clone represented naïve B-lymphocytes, which have not been in contact with antigens and do not have mutations in the DNA-variable sequence region of immunoglobulin heavy chains. Unmutated CLL is characterized by an aggressive course.

Clinic. CLL is diagnosed mainly at the age of 50-70 years, only 10% of cases occur in people younger than 40 years. In 25% of CLL cases the disease is asymptomatic and detected accidentally during the examination (systemic lymphadenopathy, spleno-, and hepatomegaly) or laboratory tests (leukocytosis with absolute lymphocytosis in hemogram).

The disease develops gradually, slowly progressing: the leukocytosis increases, which without treatment over time can reach huge numbers ($500-1000 \times 10^9/L$), the percentage of lymphocytes increases up to 75-99%, and there is a tendency to recurrent infections, first of all the infections of upper respiratory tract. Sometimes laboratory changes may be the only manifestation of CLL.

In the early disease stages the anemia and thrombocytopenia are usually not detected. In the expanded clinical picture observed:

a) *the intoxication syndrome* – severe weakness, excessive sweating (especially in the evening and at night), weight loss, fever (in the absence of infectious complications);

b) *the anemic syndrome* – skin paleness, vertigo, tinnitus (icteric sclerae, jaundice in the presence of hemolysis);

c) *the syndrome of infectious complications* – recurrent infections of bacterial, viral, fungal etiology – upper respiratory tract infections (bronchitis, pneumonia, pleurisy), urinary tract, skin and soft tissue infections (the boils, abscesses, phlegmons development), often occurs Herpes zoster;

d) *the tumor proliferation syndrome* – a systemic, often symmetrical, increase of peripheral lymph nodes, mediastinal lymph nodes, abdomen (sometimes like doughy consistency conglomerates), hepato- and splenomegaly may be varying degrees of severity, in some cases there is the tonsils ring Valdeyera hypertrophy;

e) *the hemorrhagic syndrome* – petechiae, ecchymosis, bleeding mucous membranes (gums) due to thrombocytopenia;

e) *the autoimmune complications syndrome* – autoimmune hemolytic anemia (in 20-35% of patients), autoimmune thrombocytopenia (2-3% of cases), partial red cell aplasia.

There are several peculiarities of laboratory parameters in CLL:

1. Hemogram – lymphocytosis $>5.0 \times 10^9/L$ (lymphocytes), the Gumprecht's shadow cells in the blood smears are detected (lymphocytes dilapidated core); anemia and thrombocytopenia are typical for late-stage disease.

2 With the autoimmune hemolytic anemia development the direct Coombs test becomes positive.

3. Myelogram – bone marrow hyper- or normocellular, 30% of all nuclear cells – mature lymphocytes.

The International Working Group (1989) proposed criteria for the CLL diagnosis:

- absolute lymphocytosis in peripheral blood $\geq 5.0 \times 10^9/L$;
- $>30\%$ lymphocytes in the bone marrow punctate;
- immunophenotype confirmation of B-cell clone leukemic lymphocytes: CD5⁺, CD10⁻, CD19⁺, CD23⁺, CD43^{+/-}, FMC7⁻, with low CD20⁺, CD22⁺, CD79b⁺ expression, the numerous one type of light chain predominance (clonal kurtosis) ($\kappa/\lambda > 3:1$ or $< 1:2$) and low density of surface immunoglobulin (sIgD±sIgM).

There are 2 parallel classifications, used in clinical practice, describing the CLL staging, risk, prediction of patients' survival.

Table 5

The CLL classification by Rai (Rai K.R. et al., 1975; Rai K.R., 1987)

Stage	Clinical features	Risk group	Average survival, years
0	Absolute lymphocytosis ($>5.0 \times 10^9/L$ in peripheral blood with $>40\%$ lymphocytes in the bone marrow).	Low	10
I	Lymphocytosis with lymphadenopathy.	Middle	6
II	Lymphocytosis with spleno- and/or hepatomegaly, lymph nodes are enlarged or normal.	Middle	4-6
III	Lymphocytosis with anemia (Hb <110 g/L or hematocrit $<33\%$); lymph nodes and spleen are enlarged or normal.	High	2
IV	Stage 0-III plus thrombocytopenia (platelets $<100 \times 10^9/L$); there can be organomegaly and anemia.	High	1,5-2

Table 6

The CLL classification by Binet (Binet J.L., 1981)

Stage	Clinical features	Risk group	Average survival, years
A	Hemoglobin > 100 g/L, platelets $> 100 \times 10^9/L$; less than 3 lymph areas are injured.	Low	> 9
B	Hemoglobin > 100 g/L, platelets $> 100 \times 10^9/L$; more than 3 lymph areas are injured.	Middle	5
C	Hemoglobin <100 g/L and/or platelets $<100 \times 10^9/L$.	High	2

For the CLL diagnosis and its staging, determining treatment strategy the common blood test (WBC, RBC, and platelets) must be performed. Other necessary laboratory and instrumental tests include: blood chemistry (creatinine, urea, bilirubin, transaminase activity, the LDH level, uric acid, etc.), proteinogram with focusing on albumin content, direct Coombs test (for suspected hemolysis), the chest x-ray, computed tomography of the chest, abdomen, pelvis, electrocardiogram, immunophenotype status, cytogenetic/FISH studies (to identify chromosomal aberrations), β_2 -microglobulin serum level, molecular genetic studies to establish the mutational status of IgVH.

Unfavorable prognostic factors in CLL include the LDH, β_2 -microglobulin, thymidine kinase high levels, dissolved CD23, a doubling lymphocytosis in hemogram, unmutated status of the immunoglobulin heavy chain (IgVH), increased expression of ZAP-70 protein in leukemic cells and CD38 on the cell surface, the presence of cytogenetic abnormalities: del(17p), del(11q) and t(11q; v).

Treatment. One of the most important fundamental issues in the CLL treatment is the specific therapy start. Tactics "watching and waiting" is caused by primarily slow and benign disease course (life expectancy of patients with low-risk (Stage 0(A) by Rai, Binet) is over 10 years). However, it is appropriate only for patients at an early CLL stage and can be used until the progression signs appear.

Generally accepted indications for specific cytostatic therapy start are:

1. The general intoxication symptoms presence – weakness, sweating more than 1 month, weight loss for no apparent reason more than 10% in 6 months, fever above $38^{\circ}C$ more than 2 weeks.
2. The anemia, thrombocytopenia presence, caused by the bone marrow metaplasia with leukemic cells, displacing normal hematopoiesis (stage III-IV according to Rai or stage C by Binet).
3. The leukocytes absolute number increase during the last 6 months in two times.
4. Progressive hepatosplenomegaly or massive lymph nodes enlargement.

5. Autoimmune complications (anemia, thrombocytopenia).
6. Richter's transformation.
7. Recurrent infectious complications.

The B-CLL treatment includes alkylating agents: leukeran, cyclophosphamide. Leukeran (chlorambucil, chlorbutin) is administered as monotherapy or in combination with prednisolone: leukeran 4-8 mg/m² daily for 4-8 weeks under the leukocyte level control with/without prednisolone at a dose of 30 mg/m². Cyclophosphamide 2-3 mg/kg, per os daily or 400 mg i/v every other day (total course dose 8-12 mg) with/without prednisolone at a dose of 30 mg/m².

The purine analogues such as fludarabine (Fludara) use is effective at a dose of 25 mg/m² intravenously or 40 mg/m² per os for 5 days every 4 weeks.

Alternative drugs in the CLL treatment are monoclonal antibody directed against the antigen CD52 (MabKampat, Alemtuzumab), CD20 (Rituximab, MabThera).

The PCT schemes often used in CLL treatment:

1. COP: vincristine 1.4 mg/m² intravenous the 1st day, cyclophosphamide 400 mg/m² i/v during 1-5 days, prednisone 40 mg/m² per os 1-5 days every 3 weeks.
2. FC: fludarabine 25-30 mg/m² intravenous or 40 mg/m² per os during 1-3 days, cyclophosphamide 250-300 mg/m² intravenous 1-3 days every 4 weeks.
3. FCR: fludarabine 25 mg/m² intravenous or 40 mg/m² per os 1-3 days, cyclophosphamide 250 mg/m² intravenous 1-3 days, rituximab 500mg/m² intravenous drip 1st day (the 1 st course the rituximab dose is 375 mg/m²) every 4 weeks.
4. CFAR: cyclophosphamide 250 mg/m² IV during 3-5 days, fludarabine 25 mg/m² IV or 40 mg/m² per os 3-5 days, alemtuzumab 30 mg IV drip (≥2 h) 1, 3, 5 days, rituximab 375 mg/m² IV drip 1st day every 4 weeks.

Prognosis. The CLL nature, its sensitivity to specific therapies, patients' survival depends on the presence of unfavorable prognosis factors, which include: age over 70, high leukocytosis at diagnosis ($> 50 \times 10^9/L$), a leukocytes number doubling number in peripheral blood less than 12 months, unmutated status «u-CLL» and its associated expression of CD-38 and ZAP-70, cytogenetic abnormalities del 11q, del 17p, treatment resistance.

Test evaluation and situational tasks.

Choose the correct answer/statement:

1. Specify the most typical clinical symptoms of chronic lymphocytic leukemia stage I according to classification Rai-Binet:
 - A. Enlarged lymph nodes
 - B. Anemia
 - C. Hemorrhagic syndrome
 - D. Hemolytic crisis
 - E. Hepatosplenomegaly
2. Morphological diagnosis of Hodgkin's disease is characterized by the presence of the following cells in the lymph node histological preparations:
 - A. Reed-Berezovsky-Sternberg cells
 - B. Pirogov-Langans cells
 - C. Prolymphocytes
 - D. Lymphoblasts
 - E. Botkin cells
3. Chronic lymphocytic leukemia - a malignant neoplasm of the hematopoietic system, the substrate of which are:
 - A. Mature B lymphocytes
 - B. Early progenitor of cells myelopoiesis
 - C. Pluripotent hematopoietic cells that are not able to mature

- D. Plasma cells
- E. Blasts

4. Male, 46 years, complains of itching, sweating, especially at night, fever up to $38,6^{\circ}\text{C}$. Objectively: on the skin traces from itching, supraclavicular lymph nodes up to 2 cm in diameter, tightly-elastic, not soldered to the skin. What is most informative method of research for the diagnosis?

- A. A biopsy of enlarged lymph nodes
- B. Complete blood count
- C. Plain radiography of the chest
- D. Immunogram
- E. Sternal puncture

5. Woman 28 years, complains of weakness, periodic rate increase blood pressure and body to $39,0^{\circ}\text{C}$, sweating more at night, weight loss. Objectively: skin and mucous membranes pale, palpable cervical, supraclavicular and inguinal lymph nodes up to 1,5-2 cm, not soldered to surrounding tissues, dense, painless. In CBC: red blood cells $3,0 \times 10^{12}/\text{L}$, hemoglobin 90 g/L, CI 0.8, leukocytes $13,0 \times 10^9/\text{L}$, eosinophils - 3%, bands - 9%, segments - 78%, lymphocytes - 7%, monocytes - 3%, ESR 48 mm/h. There was a suspicion of Hodgkin's disease, lymph node biopsy is designed. The presence of probable changes in its study?

- A. Reed-Sternberg cells
- B. proliferation of lymphocytes, lymphoblasts
- C. Proliferation of prolymphocytes and lymphoblasts
- D. Proliferation of lymphocytes and plasma cells
- E. Proliferation of lymphocytes and prolymphocytes

6. The patient, 34, was hospitalized with complaints of enlarged neck lymph nodes, subfebrile temperature during the last 2 months, increased sweating. The biopsy was taken. In punctate of the lymph node – Reed-Sternberg cells. Diagnosis: lymphogranulomatosis. What diagnostic method is appropriate to use to determine the prevalence of tumor?

- A. Positron emission tomography Computer
- B. X-ray study
- C. Thermography
- D. Lymphography
- E. Angiography

7. Patient M., 63 years, during routine preventive examination in the clinic revealed: enlarged cervical, axillar and inguinal lymph nodes, liver + 3 cm below the costal arch, enlarged spleen (13 cm in diameter). Complete blood count: RBC $3,6 \times 10^{12}/\text{L}$, HGB - 121 g/L, white blood cells - $32 \times 10^9/\text{L}$, eosinophils 3%, bands 2%, segments-33%, lymphocytes-59%, monocytes 3%, ESR 21 mm/h. Your preliminary diagnosis?

- A. Chronic lymphocytic leukemia.
- B. Liver cancer.
- C. Cirrhosis.
- D. Tuberculous lymphadenitis.
- E. Lymphogranulomatosis.

8. Male 41 years old, hospitalized in the infectious department with a diagnosis of follicular tonsillitis. Enlarged submandibular lymph nodes to 1.5-2 cm. The body temperature - $38,8^{\circ}\text{C}$, the skin and mucous normal color. Pulse - 105 / min., Blood pressure - 140/80 mm Hg. In CBC: RBC - $2,5 \times 10^{12}/\text{L}$, HGB - 92 g/L, CI - 1.1; WBC - $36,0 \times 10^9/\text{L}$, blasts - 69%, bands -1%, segments - 15%, lymphocytes - 13%, monocytes - 2%, ESR - 49 mm/h. What is the likely diagnosis?

- A. Acute leukemia

- B. leukemoid reaction
- C. Chronic lymphocytic leukemia
- D. Chronic myeloid leukemia
- E. Acute agranulocytosis

9. Male 62 years, has chronic lymphocytic leukemia for a few years. Drug therapy was not prescribed. He complains of weakness. Objectively: condition is satisfactory, the body temperature of 36,7°C. The enlarged cervical, supraclavicular, axillary lymph nodes up to 2 cm. In CBC: RBC - $3,4 \times 10^{12}/l$; HGB - 113 g/l; CI - 0.98; WBC - $48 \times 10^9/L$, eosinophils - 1%, bands - 2%, segments - 26%, lymphocytes - 64%, monocytes - 7%, PLT $167 \times 10^9/L$, ESR - 53 mm/h, Botkin shadows. What is your further therapeutic tactic patient?

- A. Medical observation without treatment
- B. Prednisolone
- C. Chlorambucil
- D. Plasmapheresis
- E. Blood transfusion

10. Woman 44 years old, came to the doctor with complaints of general weakness, pale skin, itching, raising the temperature to 37.3°C. In the right supraclavicular area enlarged lymph nodes. X-ray: enlarged bronchopulmonary lymph nodes. The abdomen is soft on palpation. Liver +3 cm. What do you think the diagnosis of the patient?

- A. Lymphogranulomatosis
- B. Tuberculosis
- C. Sarcoidosis
- D. Metastatic tumor
- E. Chronic myeloid leukemia

Real-life situations to be solved:

1. Patient 31 years old, went to the doctor complaining of enlarged lymph nodes above the clavicle on the left. During the physical examination: palpable enlarged painless lymph nodes on the left in the supraclavicular area. The liver and spleen are not enlarged. A blood test: hemoglobin - 120 g/l, leukocytes - $9.6 \times 10^9/L$, 1 eosinophils 1%, bands - 5%, segments - 70%, lymphocytes 18%, monocytes 6%, ESR - 55 mm / h, PLT $58 \times 10^9/L$. X-ray of the chest at the top of the right lung is determined the infiltration, which contrasts with the lung tissue. What test is needed to confirm the diagnosis? What is the most likely diagnosis?

2. Patient P., 72 years old, was hospitalized in the hematology department with complaints on general weakness, sweating, weight loss, swollen lymph nodes on the neck to the size of a hen's egg. Objectively: skin and visible mucous membranes are pale, palpable enlarged cervical and axillary lymph nodes, the size of 4x4 cm, paste-like consistency, painless, mobile, the skin over them is not changed. Breathing is vesicular in the lungs. The heart rate 89 beats/min. The liver sizes are 15x14x13 cm, the spleen protrudes under the costal arch on 3 cm, soft-elastic, painless on palpation. The hemogram: erythrocytes - $3.5 \times 10^{12}/l$, Hb - 98 g/l, the color index - 0.8; MCV - 95,8 fl, platelets - $96 \times 10^9/l$, white blood cells $318.0 \times 10^9/l$, bands 3%, segments 8%, eosinophils 1%; basophils 0% prolymphocytes 10%, lymphocytes 76%, monocytes 2%, ESR - 30 mm/h, the shadows of disrupted cells. Immunological assessment of the peripheral blood detected clonal proliferation of B cells $CD5^+10^{-}19^+20^+23^+$. What is the most likely diagnosis?

Recommended literature:

A. Main:

1. Davidson's Principles and practice of medicine (21st revised ed.) / by Colledge N.R., Walker B.R., and Ralston S.H., eds. – Churchill Livingstone, 2010. – 1376 p.
2. Harrison's Principles of Internal Medicine, 19th Edition / by Longo D.L., Kasper D.L., Jameson J.L. et al. (eds.). – McGraw-Hill Professional, 2015. – 4012 p.
3. The Merck Manual of Diagnosis and Therapy (nineteenth Edition)/ Robert Berkow, Andrew J. Fletcher and others. – published by Merck Research Laboratories, 2011.

B. Additional:

1. H.Löffler, J.Rastetter, T.Haferlach. 6th edition. Atlas of clinical hematology. Springer Berlin Heidelberg New York, 2006, - 429 p.
2. Hoppe RT, Advani RH, Bierman PJ, Bloomfield CD, Buadi F, Djulgegovic B. Hodgkin disease/lymphoma. Clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. Mar 2006;4(3):210-30.

Composed by

as. Lymanets T.V.