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МЕТОДИЧЕСКАЯ РАЗРАБОТКА
Для проведения занятия со студентами
3 курса ФПСЗС, обучающихся на английском языке
по патологической физиологии

Тема: **Гемобластозы. Лейкозы**

Theme: **Hemoblastosis. Leukemia**

Время 3 ак. часа

1.Actuality of the theme. Steady growth of number of leucosis among the population of many countries of the world and high lethality demand steadfast attention to the given pathology. Preventive measures have the large significance in struggle with leucosis. Therefore it is important for the future doctor to acquire existing submissions about etiology of leucosis (chemical cancerogens, ionizing radiation, virus infection). Each form of leucosis differs by characteristic shifts of cytostructure of peripheral blood and bone marrow. On these features differential diagnostics of leucosis is constructed. It is necessary to mark that the therapy of leucosis mainly pathogenetic. The deepening of our submissions about separate chains of pathogenesis will promote perfecting of purposeful treatment.

Learning goals of the lesson: Consider formation of tumor transformation under the influence of various factors. To study etiology and pathogenesis of different types of leukemia.

Educational goals of the lesson: formation of scientific outlook and theoretical basis of future specialists on the basis of fundamental knowledge and the latest achievements of pathological physiology.

Objectives of the lesson:

1. To know etiology and pathogenesis of acute and chronic leukemia.
2. To know peripheral blood in various forms of leukemia.

To repeat the following questions from related disciplines to ensure absolute mastery of the material:

1. Scheme of hemopoiesis (histology, cytology, embryology disciplines).
2. Quantitative parameters of blood (normal physiology discipline).

Control questions of the lesson:

1. Hemoblastosis, general characteristics.
2. Leukemia: definition, general characteristics, principles of classification, tumor nature of leukemia.
3. Etiology of leukemia: role of viruses, chemical carcinogens, ionizing radiation, t abnormal expression of oncogenes.
4. Features of leukemia cells.
5. Acute leukemia: classification. Features of hematopoiesis and peripheral blood picture.
6. Chronic leukemia: classification. Features of hematopoiesis and peripheral blood picture.
7. Main disorders in the body with leukemia, their mechanisms.
8. Principles of diagnosis and therapy of leukemia.

Calculation of study time

Total study time 3 ac.hours

№ п/п	Contents	Calculation of study time
1.	Introduction. Motivational characteristic of the theme	3 minutes
2.	Written control of students on the topic of the lesson	15 minutes
3.	Interviews with students about the topic of the lesson	60 minutes
4.	Self-managed student work	15 minutes
5.	Summing up the results of the lesson	5 minutes
6.	Decision of situational tasks	20 minutes
7.	Task for the next lesson	2 minutes

Additional materials:

Hemoblastosis – is a group of malignant tumors of hematopoietic tissue and lymph organs.

According to primary tumor localization hemoblastosis divided into:

- leukemia (primary localization in the bone marrow);
- lymphoma (primary location outside of the bone marrow).

LEUKEMIA

Leukemia – is a tumor originating from hematopoietic cells in the bone marrow, which the basis of development is the uncontrolled growth of cells with a predominance of proliferation over the differentiation and formation the foci of abnormal hematopoiesis in organs and tissues that are normally not involved in hematopoiesis.

General characteristics of leukemia:

- leukemia is characterized by the proliferation of primary atypical cells in the bone marrow suppression with of normal hematopoietic tissue;
- the ability of leukemic cells for invasion and metastasis leads to subsequent dissemination into the peripheral blood, spleen, lymph nodes and other organs;
- leukemias are often characterized by leukocytosis, presence of atypical and immature cells in the peripheral blood (but not in all forms and not in 100% of cases).

Principles of leukemia classifications

The following principles are given for leukemia classifications:

1. degree of differentiation (maturity) of leukemic cells;
2. histogenesis and cytogenesis of tumor cells;
3. number of blast cells in peripheral blood.

1. According to the degree of differentiation (maturity) of leukemic cells are distinguished:

- acute leukemia – tumor from BM with complete loss of ability of stem blood cells to differentiation. Is characterized by the rapid increase of immature blood cells.
- chronic leukemia – tumor from BM with partial delayed of ability of stem blood cells to differentiation. Is characterized by the excessive production of relatively mature WBC and their accumulation.

The defining characteristic is not the speed of process current; it is the tumor substrate (the main mass of components of the tumor cell). If the main mass of cells is represented blasts it is acute leukemia; in chronic leukemia – the tumor cells are mature and maturing elements.

2. According to the histogenetic characteristics of leukemic cells:

- neoplasms from the cells of lymphoid lineage;
- neoplasms from the cells of myeloid lineage.

3. According to the number of leukocytes and blast cells in the peripheral blood acute leukemias are divided into:

- leukemic – high level of WBC sometimes more than $50-80 \times 10^9/l$, a large number of blast cells;
- subleukemic – leukocytosis less than in previous type, blast cells are found in small amounts (3-5%);
- aleukemic – WBC normal, blast cells are not found in the blood;
- leukopenic – WBC below $4 \times 10^9/l$, a small number of blast cells.

Etiology of leukemia

Etiology is unclear in most cases of leukemia.

Theories of leukemia occurrence:

- chemical theory
- radiation theory
- viral theory
- genetic theory

Chemical theory

In experiment: induction of leukemia in animals was made by introducing carcinogens (dimetilbenzantratsen , methylcholanthrene , etc.), metabolites of tryptophan and tyrosine.

The risk of acute leukemia is increased in people with long occupational exposure to benzene and volatile organic solvents (drivers, workers leather and shoe industry, etc.). Exposure to phenylbutazone, arsenic, thorotrast, and chloramphenicol may be related to the future development of leukemia. In most cases, bone marrow aplasia caused by drug exposure is the initial event, and acute leukemia evolves later. Cytotoxic therapy, especially with alkylating agents such as melphalan, chlorambucil, and cyclophosphamide, increases the risk for leukemia. The risk seems to be related to the total dose of the alkylator agents that are received.

The incidence of acute myeloid leukemia is increased 1.3-2 times in smokers, presumably because of exposure to carcinogens, such as benzene, in tobacco smoke.

Radiation theory

Ionizing radiation is the cause of radiation leukemia in laboratory animals (single (>2 Gr) or chronic exposition). There are data about increase of the number of cases of leukemia in children, exposed to radiation and in patients who underwent X-ray and radioactive isotope treatment. Increased incidence of AML and CML residents of Hiroshima and Nagasaki at the radiologists, patients treated for malignant tumors with high doses of X-rays, yttrium, radium.

Viral theory

Three lymphotropic viruses – human T-cell leukemia virus-1 (HTLV-1), Epstein-Barr virus (EBV), and Kaposi sarcoma herpesvirus/human herpesvirus-8 (KSHV/HHV-8) – have been implicated as causative agents in particular lymphomas. HTLV-1 is associated with adult T-cell leukemia/lymphoma. EBV is found in a subset of Burkitt lymphoma, 30% to 40% of Hodgkin lymphoma (HL), many B-cell lymphomas arising in the setting of T-cell immunodeficiency, and rare NK-cell lymphomas. In addition to Kaposi sarcoma, KSHV is uniquely associated with an unusual B-cell lymphoma that presents as a malignant effusion, often in the pleural cavity.

Genetic theory

CLL has dominant and recessive types of inheritance. Several diseases have predisposing to spontaneous chromosome breakage and nondisjunction of somatic or sex chromosomes (Down, Klinefelter, Turner syndrome, Fanconi anemia etc.)

Philadelphia Chromosome. This chromosome appears as a result of deletion of the chromosome of the 22nd pair and translocation of the separated segment to the 9th pair (in 90% of the patients). The c-abl oncogene at 9q34, coding for the tyrosine protein kinase p145, is translocated to the bcr (breakpoint cluster region) on 22q. This results in a new and abnormal fusion gene, producing bcr/c-abl mRNA. This mRNA synthesizes a potent tyrosine protein kinase p210 unique to chronic myelogenous leukemia. The p210 protein may be instrumental in the genesis of CML.

Translocation of the 8th chromosome segment to the 14th has the same frequency in lymphoma of Burkitt, most likely because of the influence of Epstein-Barr's virus. In follicular lymphoma can be found mutation t(14;18) with formation of fusion gene resulting from translocation IgH-bcl-2 (IgH – immunoglobulin heavy chain enhancer) that is an inhibitor of apoptosis.

Pathogenesis of leukemia

Stages of leukemia development:

- Initiation
- Promotion
- Infiltration
- Progression
- Metastasis

Initiation

Pathogenic factor (radiation, viruses, etc.) acts on hematopoietic stem cells as a result is the mutation. The mutation leads to the transformation of proto-oncogenes to oncogenes and anti-oncogenes inactivation. To initiate tumor growth, as a rule, require activation of two or more oncogenes in combination with dysfunction of anti-oncogenes. Due to the malignant transformation the hematopoietic cells go out of control of regulatory systems, their division is activated and differentiation is suppressed.

Promotion

Activation and hyperproliferation of leukemic cells under the promoter to form a clone of leukemic cells those are identical to phenotype and genotype (monoclonal stage)

Infiltration

Dissemination of leukemic cells in the bone marrow with inhibition of normal hematopoiesis

Progression

Instability of the cell genetic apparatus of the tumor substrate leads to qualitative changes: disruption of the chromosomes structure, aneuploidy and derepression of previously active genes. These changes lead to the appearance of new clones of tumor cells that differ in phenotype and genotype (polyclonal stage). Among the new clones (formatted in the organism life and under the influence of therapeutic agents used in chemotherapy) "selected" the most autonomous clones, which leads to a "malignancy" of the disease. In polyclonal stage leukemic cells become resistant to cytotoxic therapy.

Metastasis

Pathological focuses of bone marrow are formed due to the ability of leukemic cells to the invasion, intra- and extravasion, migration by the vascular system, implantation and proliferation in different tissues and organs

Evidence of tumor nature of leukemia

Tumor nature of leukemia confirmed the presence of the general signs of uniting leukemias and tumors:

- impaired cells ability to differentiate;
- proliferation (violation of realization of apoptosis);
- morphological and metabolic cell anaplasia;
- tumor progression;
- infiltrative growth;
- ability to metastasize;
- cachexia;
- frequent death of the organism.

Features of leukemic cells

Morphological features of leukemic cells

1. Size:
 - increased by 2-3 times or reduced to the size of the lymphocyte;
 - anisocytosis.
2. Nucleus:
 - increased;
 - contours deformed;
 - coarse chromatin, its amount increased;
 - vacuolization and segmentation of nucleus.
3. Nucleoli:
 - the number increased to 8 or more;
 - the size is increased to 1/3-1/2 of the nucleus, the more nucleoli – the more malignant process.
4. The cytoplasm:
 - sharp basophilia;
 - vacuolization;
 - grains in the cytoplasm (acute leukemia monoblastic);
 - azurophilic grain;
 - Auer rods- formation in the form of sticks that resemble crystals.

Azurophilic grain and Auer rods are found not in all forms, more often – in AML.

Cytochemistry features of leukemic cells

Blood cells contain various enzymes, fats, and other substances that can be identified by cytochemical means.

The most important cytochemical studies in the study of acute leukemia are myeloperoxidase (MPO), nonspecific esterase (NSE), PAS, and acid phosphatase (AP).

Myeloperoxidase (MPO) – myeloperoxidase is an enzyme located in the granules of myeloid and monocytic cells. Myeloperoxidase is the most important marker distinguishing myeloid from lymphoid blasts and never founded in lymphoid cells.

Nonspecific esterase (NSE) – is an enzyme that founded in large amounts in monocytic cells, in minor concentrations in myeloid or lymphoid cells. NSE is used to identify monocytes.

PAS (periodic acid Schiff stain) – demonstrates glycogen and related mucopolysaccharides. Myeloid or monocytic blasts are typically weakly positive or negative. A granular PAS is characteristic for lymphoblastic leukemia. PAS staining is positive in the erythroblastic leukemias.

Glycogen distribution pattern is important for differentiation of myelo- and lymphoblasts. In AML it has diffuse distribution, in ALL – granular.

Acid phosphatase (AP) – positive reaction in T-cell acute lympholeukemia and extremely positive in acute acute promyelocytic leukemia

Tartrate-resistant acid phosphatase (TRAP) is one of acid phosphatase isoenzymes, and important diagnostic feature of hairy cell leukemia.

CML is characterized by reduction in myeloperoxidase activity, acid and alkaline phosphatase. Decrease in alkaline phosphatase in neutrophils differs CML from leukemoid reaction myeloid type.

Cytogenetic features of leukemic cells

Cytogenetic chromosomal analysis and DNA ploidy studies are important diagnostic and prognostic factors in evaluating leukemia. Chromosomal abnormalities are detected in 70-80% of patients with acute leukemia. Many genetic abnormalities typical for specific nosological forms and confirm their clonal origin. This fact is used for diagnostic and differential diagnostic purposes.

Immunophenotypic features of leukemic cells

Immunophenotyping of blasts permit to determine the presence or absence of CD-markers (cluster of differentiation) on blast cells. In their totality can be determined the origin and the degree of differentiation of leukemic clone. Immunophenotyping is use antibodies (usually monoclonal) to various cell surface and cytoplasmic proteins.

Variants of leukemia-associated phenotypes (CD-markers), presented in Table 16.

Table 16. Cases of some leukemias and associated immunophenotype

Type of leukemia	Immunophenotype
Undifferentiated acute myeloblastic (M0)	CD13, CD33, CD34, CD117, HLA-DR
Acute myeloblastic leukemia with maturation (M2)	CD13, CD33, CD117, HLA-DR
Acute myelomonocytic leukemia (M4)	CD13, CD33, CD14, CD15, HLA-DR
Acute erythroid leukemia (M6)	CD13, CD33, CD36, CD71, HLA-DR

Clinical manifestations

The main syndromes in leukemia:

- anemic
- hemorrhagic
- infectious
- metastatic (hyperplastic syndrome)
- intoxication
- osteo-arthritis

Anemic syndrome is developed due to:

- oppression of erythropoiesis;
- supplantation of erythropoiesis;
- short-life of RBC (defect of cells);
- destroyed of RBC and its stem cells by antibodies;
- concurrent uptaking by tumors cells of substrate needed for erythropoiesis.

Hemorrhagic syndrome is developed due to:

- oppression of megakaryocytopoiesis → thrombocytopenia;
- thrombocytopathy;
- destroyed of platelets and its stem cells by antibodies;

- defect in plasmatic factors of hemostasis → coagulation disorders.

Infectious syndrome is developed due to:

- oppression of granulocyto- and lymphopoiesis;
- structural and functional defect of cells for nonspecific resistance (granulocytes, monocytes, NK);
- structural and functional defect of cells for specific immunity (lymphocytes).

Metastatic (hyperplastic syndrome) is a results of metastasis of leukemic cells to the other organs, with proliferation of tumors cells and enlargement of these organs – lymphadenopathy, hepatomegaly, splenomegaly, tonsil and gum hyperplasia). Leukemic infiltration may occur in skin, CNS (neuroleukemia), mammary glands and ovaries.

Intoxication by products of cells disintegration (nucleoproteins) is a result of cell death (norm and leukemic cells). Symptoms: fever, loss of weight, fatigue

Tumor lysis syndrome – is a group of metabolic complications that can occur after treatment of leukemias (also in lymphomas) and is caused by the breakdown products of dying tumor cells. From destroyed tumor cells release intracellular ions and large amounts of metabolic byproducts (includes potassium, phosphate and nucleic acids) into the systemic circulation. They result in metabolic abnormalities like hyperkalemia, hyperphosphatemia, hyperuricemia, hyperuricosuria, hypocalcemia, and consequent acute uric acid nephropathy and renal failure.

Osteo-arthritis syndrome is caused by accumulation of cancer cells in the BM. It leads to the increase in pressure in BM and cell death, which manifested by painful of bones, joints.

ACUTE LEUKEMIA

Acute leukemia – is a tumor originating from bone marrow, with complete loss of the ability of hematopoietic cells to differentiate at the level of blasts.

Morphological substrate of the tumor is blast cells (IV class on modern scheme of hematopoiesis).

Acute myelogenous leukemia (AML) is the most common type of acute leukemia in adults, 45% of all leukemias and 80-90% of acute leukemias.

Classifications of acute leukemia

Classification of acute leukemias is made by French-American-British (FAB) working hematologists group on the basis morphological and cytochemical characteristics of blast cells.

The French-American-British (FAB) classification of AML:

- M0 – Undifferentiated acute myeloblastic
- M1 – Acute myeloblastic leukemia with minimal maturation
- M2 – Acute myeloblastic leukemia with maturation
- M3 – Acute promyelocytic leukemia
- M4 – Acute myelomonocytic leukemia
- M4 eos – Acute myelomonocytic leukemia with eosinophilia
- M5 – Acute monocytic leukemia
- M6 – Acute erythroid leukemia
- M7 – Acute megakaryoblastic leukemia

Revised WHO classification of acute leukemia incorporates parameters which include morphology, cytochemistry, immunophenotyping, cytogenetics, molecular genetics (which are related to prognosis) and clinical features. The number of blasts necessary for the diagnosis is more than 20% in bone marrow when compared to 30% in FAB classification. AML is classified into seven major categories:

- Acute myeloid leukemia with recurrent genetic abnormalities
- Acute myeloid leukemia with myelodysplasia-related changes
- Therapy-related myeloid neoplasms
- Acute myeloid leukemia, not otherwise specified
- Myeloid sarcoma
- Myeloid proliferations related to Down syndrome
- Blastic plasmacytoid dendritic cell neoplasm

The French-American-British (FAB) classification of ALL includes:

L1 – ALL with microlymphoblasts. Around 25 to 30% of adult cases and 85% of childhood cases of ALL are of this subtype. In this type small cells are seen with regular nuclear shape, homogeneous chromatin, small or absent nucleolus, scanty cytoplasm.

L2 – ALL with typical blasts. Around 70% of adult cases and 14% of childhood cases are of this type. The cells are large and of varied shapes with irregular nuclear shape, heterogeneous chromatin, large nucleolus.

L3 – ALL with macrolymphoblasts. This is a rarer subtype with only 1 to 2% cases. In this type the cells are large and uniform with vacuoles (bubble like features) in the cytoplasm overlying the nucleus.

WHO proposed a classification of ALL used the immunophenotypic classification that includes:

- Acute lymphoblastic leukemia/lymphoma (L1 and L2);
- Precursor B acute lymphoblastic leukemia/lymphoma;
- Precursor T acute lymphoblastic leukemia/lymphoma;
- Burkitt's leukemia/lymphoma (L3);
- Biphenotypic acute leukemia.

Features of hematopoiesis in acute leukemia:

- more than 20% blasts in the bone marrow (the international diagnostic criteria);
- inhibition of erythro- and megakaryocytopoiesis.

Features of peripheral blood picture in acute leukemia:

- anemia,
- thrombocytopenia,
- the WBC count although usually high, leukocytosis varying from 10 to $200 \times 10^9/l$,
- atypical blasts is the main mass of the cells,
- hiatus leukaemicus – the absence of maturing forms between blasts and mature cells,
- increased ESR.

In 30-50% of cases, the number of WBC and blasts reduced, blasts are rare or absent in the formula (leukopenic or aleukemic type of leukemia).

Clinical stages of acute leukemia:

Acute leukemia in the development passes the following clinical stages:

Debut (first attack) – is the time period from the occurrence of the first clinical and hematological disease symptoms to diagnosis and start of treatment to obtain the effect of the therapy.

Alternating remissions and relapses.

Remission – is weakening the manifestations of the pathological process under the influence of cytostatic therapy. Distinguish between complete and incomplete remission.

Complete remission characterized by:

- normalization of clinical parameters, peripheral blood and bone marrow for at least 1 month;
- bone marrow: blast cells in BM $\leq 5\%$, and none can have a leukemic phenotype (eg, Auer rods), lymphocytes $< 30\%$;
- hemogram: blasts – absent, granulocytes $\geq 1.5 \times 10^9/l$, Tr $\geq 100 \times 10^9/l$, Hb $\geq 100g/L$ (male), $\geq 90g/L$ (female and children);
- clinical: disappear of pathological symptoms;
- subjective: no complaints.

State of complete remission for 5 years or more is called recovery.

Incomplete remission characterized by normalization of clinical parameters, peripheral blood and bone marrow, but blast cells in BM $\leq 20\%$

Relapse – is the return of leukemic process after remission (bone marrow, outside bone marrow, combined).

Bone marrow relapse is divided into:

- aleukemic – blasts in BM $> 20\%$, in peripheral blood – absence;
- leukemic – blasts in BM $> 20\%$ and in peripheral blood.

Outside bone marrow (local) relapse is the presence of leukemic infiltrates outside BM (in lymph nodes, spleen, skin, etc.).

Terminal stage of acute leukemia – is the final stage of tumor progression, comes with complete depletion of normal hematopoiesis and resistance to cytostatic therapy. The most often causes of patient's death are infectious and inflammatory complications, bleeding, hemorrhage in internal organs.

Acute myeloblastic leukemia (AML)

The tumor arises from the transformed progenitor cells of myelopoiesis (II class on modern scheme of hematopoiesis).

Substrate tumor – myeloblasts (IV class on modern scheme of hematopoiesis).

Peripheral blood picture:

- anemia,
- thrombocytopenia,
- myeloblasts is the main mass of the cells,
- hiatus leukaemicus

Bone marrow: numerous myeloblasts with azurophilic granules and 1-2 Auer rods.

Cytochemical features of myeloblasts are presented in Table 17.

Table 17. Cytochemical features of myeloblasts in different type of AML by FAB classification

	M1	M2	M3	M4	M5	M6	M7
MPO	+	+	+	+	- / +	-	-
NSE	-	-	- / +	+	++	+	+ / -
PAS	-	-	-	-	- / +	+	+

Manifestations:

Bone marrow failure is due to replacement of normal marrow hematopoietic cells by leukemic blast cells. All or any of the three cell lines are decreased, which results in anemia, neutropenia and thrombocytopenia. Anemia causes fatigue, weakness (directly related to the degree of anemia). Neutropenia results in life-threatening infections by bacteria or opportunistic fungi, *Pseudomonas* and commensals in different organs and systems. Thrombocytopenia presents as bleeding manifestations in the form of petechiae, atraumatic ecchymoses, gum, nasal, urinary tract bleeding.

Leukostasis – stasis of blood flow may develop when the blast count in the peripheral blood is above $50 \times 10^9/l$. It is more common in AML than ALL because myeloblast is larger and expresses adhesive proteins. Cerebral leukostasis may cause headache, confusion and visual disturbances.

Disseminated intravascular coagulation syndrome is observed in AML-M3 (promyelocyte leukemia).

Extramedullary infiltration may be in organs like lymphnodes, spleen, gingiva, skin (leukemia cutis) and meninges. Gingival hypertrophy and infiltration of skin (leukemia cutis) may be found in monocytic type of AML (M4).

Splenomegaly and hepatomegaly may be found and is more common in AML.

Acute lymphoblastic leukemia (ALL)

In adults this tumor is rare; in children – is 80% of all forms of leukemia. The peak incidence occurs between the ages of 4-5 years.

The tumor arises from the transformed progenitor cells of lymphopoiesis (II class on modern scheme of hematopoiesis).

Substrate tumor - lymphoblasts (IV class on modern scheme of hematopoiesis).

Peripheral blood picture:

- anemia,
- thrombocytopenia,
- lymphoblasts is the main mass of the cells,
- granulocytopenia
- absolute lymphopenia (significantly reduced content of differentiated lymphocytes)

Bone marrow: more than 20% lymphoblasts restriction normal hematopoiesis.

Manifestations:

Symptoms are related to depressed marrow function due to infiltration by blasts. There are anemia, neutropenia and thrombocytopenia. Lymphadenopathy is present in 75% of patients. Splenomegaly is more common than hepatomegaly. Leukemic meningitis is rare and is more common in ALL (pre-B). In children with ALL metastases most commonly affects the testicles (in boys), and meninges.

CHRONIC LEUKEMIA

Chronic leukemia – is a neoplasm originating from bone marrow, with partial delay ability of hematopoietic cell to the differentiation. In chronic leukemia cells retain the ability to differentiate to the stage of maturing or mature cells.

Substrate for chronic leukemia – maturing (V class) and mature (VI class) cells.

Classifications of chronic leukemia:

Chronic leukemia is conventionally divided into 2 groups:

- myeloproliferative
- lymphoproliferative

The chronic myeloproliferative leukemia include:

1. Chronic myeloleukemia,
2. Chronic monocytic (myelomonocytic),
3. Chronic neutrophilic leukemia,
4. Chronic eosinophilic leukemia / hypereosinophilic syndrome,
5. Essential thrombocythemia (ET),
6. Polycythemia vera (PV) – erythremia,
7. Idiopathic myelofibrosis (subleukemic myelosis).

The chronic lymphoproliferative leukemia include:

Chronic B-cell leukemia:

- B-cells prolymphocyte leukemia,
- Paraproteinemic hemoblastoses:
 - ✓ Multiple myeloma,
 - ✓ Waldenstrom's macroglobulinemia,
 - ✓ Heavy chain disease,
- Hairy cell leukemia,

Chronic T-cell / NK-cell leukemias:

- T-cells prolymphocyte leukemia,
- T-cells leukemia of large granular lymphocyte,
- Aggressive NK-cell.

Features of hematopoiesis in chronic leukemia:

- partially delayed cell maturation;
- increases content of myeloid cells, particularly myelocytes metamyelocytes neutrophils in

CML;

- occurs infiltration by mature small lymphocytes in CLL.

Features of peripheral blood picture in chronic leukemia:

- anemia and thrombocytopenia develop as the disease progresses;
- WBC count varies significantly depending on the stage (from moderate leukocytosis to a significant increase in the number of leukocytes);
 - as a result of chronic leukemia progression in the bone marrow and in the blood can be increased the number of blast cells (up to blastic crisis);
 - CML is characterized by basophilic-eosinophilic association (simultaneous increase in the absolute number of eosinophils and basophils in the peripheral blood).

Clinical stages of chronic leukemia:

Chronic (expand) – is characterized by a long-compensated current.

Acceleration – is characterized by active proliferation of leukemic cells.

Terminal – occurs blast transformation, is manifested by blast crisis.

Blast crisis – is a sharp increase in the number of blast cells in bone marrow and peripheral blood (more than 20%), progression of anemia, thrombocytopenia and formation of out bone marrow leukemic

infiltrates. Blast crisis is the final phase of chronic leukemia and its clinical and hematological picture corresponds to the picture of acute leukemia.

Hematological criteria of blast crisis (WHO, 2008):

- in the bone marrow and peripheral blood more than 20% blast cells;
- extramedullary blastic proliferation;
- blast infiltration of the bone marrow histologically detectable.

Chronic myeloid leukemia (CML)

Tumor arises from hematopoietic stem cells (I-II classes on modern scheme of hematopoiesis). Inhibition of differentiation occurs at the level of maturing granulocytes.

Substrate tumor - mature neutrophils, metamyelocytes, myelocytes, promyelocytes, myeloblasts (a little) (V-VI classes on modern scheme of hematopoiesis).

Peripheral blood picture in chronic phase:

- hemoglobin, RBC count is normal, later - normochromic anemia,
- platelets are normal, possible of their increase or decrease,
- neutrophilic leukocytosis with a left shift to promyelocytes, single blast,
- basophilic-eosinophilic association.

With tumor progression to the acceleration and terminal stage increases anemia, thrombocytopenia, increases the number of blasts. In phase of blast crisis there is marked neutropenia, thrombocytopenia and pronounced increase of blasts more than 20%.

Bone marrow:

- bone marrow is hypercellular due to granulocyte increased leuko/erythroblastic ratio;
- in progress is the oppression of erythro- and megakaryocytopoiesis;
- progressively increasing the number of blast cells.

Manifestations:

Most of patients are diagnosed in the chronic phase. Common symptoms include fatigue, weight loss, low-grade fever, bone tenderness, abdominal fullness, abdominal pain (splenic infarcts), loss of appetite, night sweats, and splenomegaly. As the disease progresses, the features worsen. Appearance of blasts and promyelocytes in the peripheral blood increase splenomegaly, bone pain, thrombocytopenia (bleeding, petechiae, ecchymosis and bruising) and worsen anemia. Many patients are asymptomatic.

Erythremia (Vakeza disease, Polycythemia Vera)

Polycythemia Vera is a myeloproliferative disorder marked by erythrocytosis (increased red cell mass). The tumor arises in the transformation of the stem cell or progenitor cells of myelopoiesis.

Substrate tumor - may be the cells of 3 or 4 hemopoietic lineage: granulocytic, monocytic, erythroid, megakaryocytic.

Peripheral blood picture:

- erythrocytosis is the most prominent clinical manifestation (with a reduction of erythropoietin levels in blood and urine),
- hemoglobin increased to 180-220 g/l,
- reticulocytosis,
- can be thrombocytosis with giant forms,
- neutrophilic leukocytosis with a left shift to myelocytes,
- sharply lower ESR, hematocrit and blood viscosity increased.

Bone marrow: hypercellular with hyperplasia of all three bone marrow elements. In greatest degree damaged erythroid lineage. Decrease leuko/erythroblastic ratio due to erythroid hyperplasia.

Manifestations:

Most commonly occurs in older adults (average age = 60 years). Many of symptoms are related to sluggish blood flow caused by increased blood viscosity (increased hematocrit). Headaches, pain in the joints, spine and fingertips are associated with microvascular occlusion. It is also noted hypertension, splenomegaly (80% of patients). Thrombotic complications are common and a major factor in morbidity.

Chronic lymphoid leukemia (CLL)

In 95% of cases CLL malignant transformation is undergoing a "naive" B-lymphocyte; in remaining 5% of cases – a common lymphoid progenitors. The chronic malignant lymphoproliferative disorders originate in the bone marrow and slowly progress to involve the peripheral blood, lymph nodes, spleen, and liver.

Substrate tumor - proliferating mature and maturing lymphocytes, may be of B, T, or NK origin.

Peripheral blood picture:

- anemia, thrombocytopenia, (due to the displacement of germs from the bone marrow, and due to the formation of antibodies to them by leukemia cells),
- more often observed leukocytosis,
- absolute lymphocytosis ($>5,0 \times 10^9/l$, but usually $>15,0 \times 10^9/l$ and sometimes $> 100,0 \times 10^9/l$),
- may be prolymphocytes (from single up to 5-10%) and lymphoblasts,
- Botkin-Gumprecht shadow (destroyed in the preparation of a smear leukemic lymphocytes) – a characteristic hematological symptom of CLL.

Bone marrow:

- often diffusely replaced by small lymphocytes. Lymphocyte amount exceeds 30%, in severe cases it may be higher;
- granulocyte, erythroid, monocyte and megakaryocytic germs are narrowed;
- interstitial or nodular lymphocytes infiltration.

Manifestations:

CLL is a disease of adults; most patients are > 60 years of age.

Leukemic lymphocytes have decreased ability to reaction of blast transformation (transformation of B lymphocytes into plasma cells) and appear ability to synthesize of Ig with distorted features. As a result CLL is often accompanied by microbial complications and autoimmune hemolytic anemia.

Lymphadenopathy and splenomegaly are common especially late in the disease because small lymphocytes accumulate in the marrow, spleen, lymph nodes and liver.

The clinical course is highly variable with survival ranging from 1-20 years.

LYMPHOMAS

The malignant lymphomas constitute a heterogeneous group of neoplasms arising from the immune system and primarily involving lymphoid cells.

Classification of lymphomas

WHO-classification of tumors of lymphoid tissue (2008) allocates more than 30 varieties of mature B-cell neoplasms, and over 20 varieties of mature T / NK-cell neoplasms.

Lymphomas are classified based on the cell type and the architectural (growth) pattern: the Hodgkin and the Non-Hodgkin lymphomas.

Hodgkin Lymphoma (HL)

Classification of Hodgkin lymphoma WHO (2008):

- Nodular lymphocyte predominant Hodgkin lymphoma
- Classical Hodgkin lymphoma
- Nodular sclerosis classical Hodgkin lymphoma
- Lymphocyte-rich classical Hodgkin lymphoma
- Mixed cellularity classical Hodgkin lymphoma
- Lymphocyte-depleted classical Hodgkin lymphoma

Manifestations

Hodgkin lymphoma has a unique bimodal distribution, with the first peak being between the ages of 15 and 34 years and a second peak among individuals over 50 years.

HL is a lymph node-based malignancy and commonly presents as an asymptomatic lymphadenopathy that may progress to predictable clinical sites. More than 80% of patients with HL present with lymphadenopathy above the diaphragm, often involving the anterior mediastinum; in about 30% may be involved the spleen. Less than 10% to 20% of patients present with lymphadenopathy limited to regions below the diaphragm.

TABLE 18. The Cotswold staging classification for Hodgkin lymphoma

Stage	Description
I	Involvement of a single lymph node region or lymphoid structure (eg, spleen, thymus, Waldeyer's ring)
II	Involvement of two or more lymph node regions on the same side of the diaphragm (ie, the mediastinum is a single site, hilar lymph nodes are lateralized).
III	Involvement of lymph node regions or structures on both sides of the diaphragm. With or without involvement of splenic, hilar, celiac, or portal nodes. With involvement of para-aortic, iliac, or mesenteric nodes
IV	Involvement of extranodal site(s) beyond that designated

The commonly involved peripheral lymph nodes are located in the cervical, supraclavicular, and axillary areas; para-aortic pelvic and inguinal areas are involved less frequently. Lymph node is painless enlargement, usually firm or rubbery, often multiple and fixed in place. Disseminated lymphadenopathy is rare.

Systemic symptoms include fever, persistent fatigue, night-sweats (drenching sweats of the whole body), and weight loss. As lymphoma progresses, spread may occur to spleen, liver, bone marrow, and other organs.

HL is characterized by the presence of Reed-Sternberg cells (large size and classic binucleated structure with large eosinophilic nucleoli, with CD30 and CD15 markers).

Non-Hodgkin Lymphoma (NHL)

Classification of NHL

In the structure of Non-Hodgkin lymphomas is dominated by the B-cell neoplasms. The most common options are: diffuse large B-cell lymphoma (30% of all cases of NHL), follicular lymphoma, extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma), CLL/small lymphocytic lymphoma, mantle cell lymphoma, Burkitt's lymphoma, nodal marginal zone lymphoma, lymphoplasmacytic lymphoma (Waldenstrom macroglobulinemia). Among the mature T / NK-cell neoplasms the most common variant is peripheral T-cell lymphoma (8% of the non-Hodgkin lymphoma).

Etiology

Unclear. The most commonly associated chromosomal abnormality in NHL is the t(14;18)(q32;q21) translocation. It is found in 85% to 90% of follicular lymphomas and 25% to 30% of higher-grade B-cell NHLs. Chromosomal translocations involving 8q24 (lead to c-myc deregulation) is seen in nearly all cases of Burkitt lymphoma.

Risk Factors:

- the incidence of NHL progressively increases with age (peak approximately 60 years);
- environmental factors (pesticides and herbicides (2,4-D-organophosphates, chlorophenols), solvents and organic chemicals (benzene, carbon tetrachloride, trichloroethylene));
- viruses (EBV, HTLV-1, Kaposi sarcoma-associated herpesvirus (human herpesvirus 8) and hepatitis C virus;
- bacterial infections (*Borrelia burgdorferi* (in Lyme disease), has been detected in about 35% of patients with peripheral cutaneous B-cell lymphoma; *Campylobacter jejuni* and α -heavy chain disease are related);
- Congenital immunodeficiency (ataxia-telangiectasia, Wiskott-Aldrich syndrome, common variable hypogammaglobulinemia, X-linked lymphoproliferative syndrome and severe combined immunodeficiency) and acquired immunodeficiency (HIV infection).

Manifestations

Fever, weight loss, and night sweats, referred to as systemic B symptoms, as well as fatigue and weakness. The NHLs are a heterogeneous group of neoplasms that usually arise or present in lymphoid tissues, such as lymph nodes, spleen, and bone marrow, but they may arise in almost any tissue. Splenomegaly is seen in about 40% of patients. The most frequent sites for extranodal lymphomas are the stomach, skin, oral cavity and pharynx, small intestine, and central nervous system. Bone marrow is frequently involved, sometimes in association with cytopenias.

Peripheral blood: lymphocytosis with circulating malignant cells.

Bone marrow and peripheral blood involvement may be present, and the distinction between leukemia and lymphoma is difficult to make in some cases.

PARAPROTEINEMIC HEMOBLASTOSIS

Paraproteinemic hemoblastosis – group of diseases characterized by monoclonal proliferation of B-lymphoid cell secreting monoclonal Ig (or their fragments) are determined in serum and / or urine (paraproteins).

Paraproteins correspond to various variants of normal immunoglobulins (IgG and often IgM), but differ in uniformity of light and heavy chains or are structurally abnormal immunoglobulin molecules (fragments of heavy or light chains).

The main feature of these leukemias is to preserve the ability of B cells differentiate to the stage of immunoglobulin-secreting cells.

Paraproteinemic hemoblastoses include:

- Multiple myeloma;
- Waldenstrom's macroglobulinemia;
- Heavy chain disease (HCD).

Multiple myeloma (MM)

In multiple myeloma progenitor of B-lymphocytes undergo malignant transformation, but retains the ability to mature plasma cells. Plasma leukemic cells actively proliferate in the bone marrow and secrete myeloma paraprotein (Ig) – M-protein that enters the blood or urine.

Peripheral blood picture:

- anemia,
- often the first sign is a significant increase in the ESR to 50-90 mm/h (not for all biochemical variants of multiple myeloma),
- WBC are normal, at progress of disease may develop leukopenia,
- may appear single plasma cells (large numbers in the terminal stage).

Bone marrow: infiltration by plasma cells and oppression of normal hematopoiesis. The content of plasma cells in the bone marrow more than 10% – is one of the basic disease diagnostic criteria.

Manifestations:

MM occurs in older age groups, affects men more than women. Plasma cells are able to synthesize factors activating osteoclasts. Due to activation of the latter is destroyed bone tissue, may occur spontaneous fractures, hypercalcemia and associated lesions of the nervous, cardio-vascular systems, kidneys, gastrointestinal tract.

Reduced amount of normal plasma cells leads to disruption of formation normal Ig and syndrome of recurrent infections.

Excessive formation of immunoglobulin light chains leads to kidney damage (nephropathy myeloma). It is a 2nd place of complications leading death cause in multiple myeloma after infectious.

Bence Jones protein is a peculiar protein made by some patients with MM as a result of an excess of kappa and lambda light chains. These light chains are small and can be filtered by the kidneys, detected in the urine (proteinuria Bence-Jones)

On proteins electrophoregram in 80% of patients is determined a characteristic monoclonal peak (M-gradient). But in Bence Jones myeloma and non-secretory myeloma the serum M-gradient can not be detected.

Waldenstrom macroglobulinemia

It is characterized by production of macromolecular monoclonal paraproteins IgM by neoplastic B cells.

Peripheral blood picture:

- anemia,
- thrombocytopenia may develop at disease progress,
- possible neutropenia,
- monocytosis,
- ESR always significantly increased.

In blood serum – hyperproteinemia, electrophoregram – M gradient due to IgM.

Urine analysis: Bence-Jones protein occurs in approximately 80% of cases, but its amount is significantly less than in multiple myeloma.

Bone marrow: contains variable numbers of pleomorphic lymphoid cells.

Manifestations:

Due to the accumulation of high molecular proteins are characterized by an increase in blood viscosity, disturbance of microcirculation, predisposition to thrombosis, hemorrhagic syndrome. Usually found lymphadenopathy and hepatosplenomegaly.

Heavy chain diseases

These are B-cell lymphatic tumors with various clinical and morphological picture and secretion of heavy chains fragments (α -, γ -, μ -, δ - chains) of different Ig classes:

- α -chain disease (Seligmann's disease);
- γ -chain disease (Franklin disease);
- μ -chains disease;
- δ -chains disease.

Manifestations:

Alpha heavy chain disease typically affects the gastrointestinal system; rare cases of respiratory and lymphomatous forms have been reported. The abdominal form of alpha heavy chain disease presents as a malabsorption syndrome with weight loss, diarrhea, and abdominal discomfort due to diffuse infiltration of the small intestine mucosa and mesenteric lymph nodes by plasma cells, macrophages, and mast cells. Generalized lymphadenopathy and hepatosplenomegaly are hallmarks of the lymphomatous form. Pulmonary form is characterized by bronchopulmonary lesions and mediastinal lymphadenopathy. Proteinuria is absent.

Gamma heavy chain disease associated with rheumatoid arthritis (the most common), systemic lupus erythematosus, vasculitis, and myasthenia gravis, as well as autoimmune cytopenias, including idiopathic thrombocytopenic purpura. Manifestations of autoimmune disease often precede gamma heavy chain disease by many years.

The symptoms and signs of mu heavy chain disease are related to the associated lymphoma. Splenomegaly is almost universally present, with hepatomegaly in three-quarters of patients.

Principles of leukemia diagnosis

Identify the type of leukemia suppose a comprehensive approach and carried out by means:

- morphological,
- cytochemical,
- immunophenotyping,
- cytogenetic and molecular genetic methods.

Study the picture of peripheral blood and bone marrow (to confirm the diagnosis in suspected leukemia). Diagnosis of leukemia may also include biochemical analysis of blood serum or urine, lumbar puncture, ultrasound, x-ray, computed tomography scan and magnetic resonance imaging.

Principles of leukemia therapy

Specific chemotherapy – aims to achieve and maintain remission of the disease; consists of several stages, different for lymphoblastic and myeloid leukemia and perform according to standard schemes.

Accompanying therapy – aimed at fighting infections, reduction of toxicity in tumor lysis syndrome, reduction of toxic side effects of chemotherapy drugs.

Replacement therapy – is needed in a threatening thrombocytopenia, severe anemia, blood clotting disorders. It includes transplantation of hematopoietic stem cells, or bone marrow.

Questions for self-control of knowledge:

1. Define the concepts of "leukemia", "acute leukemia", "Chronic leukemia". What is the classification of leukemia?
2. Give the definition of "acute leukemia". What are the principles of the FAB-classification? What features of hematopoiesis and the cellular composition of peripheral blood in acute leukemia?
3. What is the hiatus leucaemicus in acute leukemia?

4. What are the criteria for clinical and hematological remission and relapse?
5. What neuroleukemia? What are its manifestations?
6. Describe the syndromes that occur in the body in leukemia.
7. At what leukemia is found, "Philadelphia" chromosome (Ph)? Describe the Philadelphia chromosome, what is the method of detection?
8. Specify the characteristics of chronic myeloid leukemia in children.
9. What are the hematological criteria for blast crisis?
10. At what leukemia and why in the peripheral blood there are shadows Botkin, basket cells?
11. What are the paraproteins?
12. At what disease appears Bence-Jones protein? Describe the disease.

Tasks for self-managed student work:

1. Tumor nature of leukemia, role of oncogenes abnormal expression.
2. Multiple myeloma.
3. Primary macroglobulinemia.
4. Heavy chain disease.

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