Ministry of Healthcare of Ukraine

Poltava State Medical University

«Approved»
at the meeting of the
Chair of Internal medicine №1
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Methodical instruction for the students self-training during preparing for practical classes (seminars)

Subject	**Internal medicine**
Module №1	**FUNDAMENTALS OF INTERNAL MEDICINE**
Topic	**Chronic Leukemias. Polycytemia Vera**
Course	**IV**
Faculty	**Medical**

***The subject of the lesson*: Chronic leukemias. Polycytemia Vera**

Chronic myeloid leukemia (CML) and polycytemia vera (PV) are the most widespread chronic myeloproliferative neoplasms. PV occurs in 2.5 per 100,000 persons, sparing no adult age group and increasing with age to rates over 10/100,000. CML incidence in Europe is 1-1.5 cases per 100 000 inhabitants per year, which is 7-20% of all leukemias adults. CML occurs in all age groups, the incidence increases with age. The mean age at time of the CML diagnosis is 60 years.

Chronic lymphoid leukemia (CLL) belongs to the most common kinds of leukemias, its share in the hemoblastoses structure is 30%; and 9% of all malignancies. CLL almost never occur in the age range under 30 years, with a progressive increase in the incidence rate after 40-50 years to reach a maximum of 85 years. Men suffer more often than women at a ratio of 2:1.

The student must know:

1. Etiology and pathogenesis of CLL, PV and CML.
2. Clinical symptoms of CLL, PV and CML.
3. Modern classification of CLL, PV and CML.
4. Methods of diagnostics of CLL, PV and CML.
5. Methods of treatment of CLL, PV and CML.

The student must be able:

1. To choose the symptoms of CLL, PV and CML from the history data.
2. In examination of the patient to choose the symptoms of CLL, PV and CML.
3. To make the scheme of investigation for the determination CLL, PV and CML.
4. To define the cause and the severity of CLL, PV and CML.
5. To assess the haemologic study results.
6. To determinate the treatment of patients with CLL, PV and CML depending on the types and degree of the disease. To estimate the efficacy of the therapy.
8. To prescribe the proper treatment for the patient with CLL, PV and CML.

The main problems of the lesson:

1. CLL, PV and CML, definition, etiology & pathogenesis.
2. Classification of CLL, PV and CML: pathogenetic classification, morphogenetic classification, international classification.
3. Clinical manifestations of CLL, PV and CML: clinical syndromes.
4. Target treatment of CML.

The contents of topic:

Chronic myelogenous leukemia (CML; chronic myeloid leukemia) (ICD-10 C92.1) – the hematopoiesis system clonal disorder, which develops from the pluripotent hematopoietic stem cell, is characterized by granulocytic leukocytosis, basophilia, thrombocytosis and splenomegaly. CML specific cytogenetic marker – Philadelphia chromosome (Ph-chromosome), it represents a balanced translocation involving the long

arms of chromosomes 9 and 22, t (9;22), produces the BCR-ABL chimeric gene, which encodes a protein p210 with the tyrosine kinase activity.

Etiology. Proven risk factor for CML is ionizing radiation. Excess morbidity occurs within 7-12 years after exposure with no significant differences in age groups. At risk of occurrence affect chemical agents, including professional factors (gasoline), drugs (cytostatics), hereditary tendency to instability of chromosomes or DNA repair system failure (Down, Patau, Klinefelter, Turner, Fanconi syndromes et al.), long-term smoking.

Pathogenesis. CML develops as a result of the Ph-chromosome formation, which is the product of the transfer of the chromosome 22 long arm's greater part on the long arm of chromosome 9 and a short terminal segment of the long arm of chromosome 9 – on the chromosome 22 long arm (reciprocal translocation). As a result, the long arm of chromosome 9 is increased in length and the long arm of chromosome 22 is shortened. This shortened long arm belonging to 22^{th} pair is called Ph-chromosome. The protooncogene ABL resides on the long arm of chromosome 9, and it encodes the protein formation with molecular weight of 145 kDa ($p145^{ABL}$) – tyrosine proteinkinase, which catalyzes the amino acids phosphorylation processes in the cell cycle. At (9, 22) translocation part of the ABL gene is fused with part of the BCR gene ($p160^{BCR}$) with the chimeric gene BCR-ABL formation on the chromosome 22, which generates a chimeric protein with a molecular mass 210 kDa – $r210^{BCR-ABL}$, which has much more powerful tyrosine kinase activity than its normal prototype $p145^{ABL}$. In such a way the cell predecessor proliferation increases, that is independent of growth factors (increased mitotic activity) with the following differentiation infringement, the adhesion of cell predecessor to stroma reduces (increase circulation cells predecessors with the extramedullary lesions formation), the apoptosis inhibition and cell genomic instability development take place.

According to CML pathogenesis the disease occurs in two phases:

- monoclonal (meets the chronic phase in clinic), benign;
- polyclonal (the acceleration phase and blast crisis in clinic), malignant.

Clinic and diagnostics. CML is often divided into three phases based on clinical characteristics: chronic phase, acceleration and blast crisis (terminal).

1. Chronic phase CML is characterized by a gradual increase in leukocytosis with a shift to myelocytes, metamyelocytes, promyelocytes and increase the number of platelets in the peripheral blood. For a long time CML is asymptomatic and can sometimes be found accidentally. During the detailed clinical manifestations the patients complain of general weakness, increased sweating, heaviness and pain in the left upper quadrant, weight loss, arising only after 1-3 years of onset. With the spleen size increasing the dyspeptic symptoms appear: discomfort, postprandial heaviness in the epigastric region of the abdomen. High leukocytosis and thrombocytosis lead to the hyperviscosity syndrome development with brain and vision dysfunction, spleen infarction, veinocclusive liver disease. An objective examination the skin paleness (in the presence of anemia), splenomegaly can be revealed.

Diagnostic criteria for chronic phase CML:

1) in hemogram – leukocytosis (15 to 800×10^9/L), the granulocytes percentage increase in the leukocyte formula up to 85-95%, possibly to blast cells (unfavorable prognostic sign), basophilic-eosinophilic association (basophils <20% and eosinophils

>5-8%); 30% of cases – mild normocytic normochromal anemia, 30% – thrombocytosis 400-800×10^9/L or more, rarely – thrombocytopenia, which is caused by the treatment;

2) myelogram – hypercellular bone marrow with an increased number of young granulocytes (percentage of myeloblasts <15%), the percentage of myeloblasts + myelocytes <30%);

3) trepanobiopsy (microscopic examination of the bone marrow) – hypercellular bone marrow with myeloid hyperplasia, leuco-erytroblast ratio is more than 10:1, in 40-50% megakaryocysis is detected;

4) cytogenetic and molecular genetic study – available Ph-chromosome t(9;22)(q34; q11) in 95-100% of metaphases and gene BCR-ABL;

5) absence of myeloid lesions in the other organs and tissues except the spleen and liver.

The chronic phase CML treatment is effective under conditions of adequate pharmacological therapy. The clinical and hematologic manifestations of the disease may be restrained for a long time.

2. The acceleration phase develops when the monoclonal stage transits into polyclonal, it characterized by decreased sensitivity to the previous specific therapy, even to full resistance. Diagnosed acceleration phase CML provided that one or more of the following symptoms, according to the ESMO recommendations (2017):

- Increasing the number of leukocytes, myelocytes, metamyelocytes, promyelocytes;
- 10-19% blast cells in the hemogram and/or myelogram;
- Progressive thrombocytosis (resistant to treatment), sometimes up to 1500-2000×10^9/L or progressive thrombocytopenia <100,0×10^9/L, doesn't caused by treatment;
- The basophils number in peripheral blood > 20%;
- The growth of the tumor clone, according to cytogenetic and molecular genetic study.

Clinically, in the acceleration phase no specific symptoms are observed. The patientas general condition may remain satisfactory. In some cases, patients complain of increasing general weakness, body temperature, the spleen enlargement. In the later stages of acceleration phases there can be pain in bones and joints, increased susceptibility to recurrent infectious processes.

3. The blast crisis phase is the terminal stage of CML.

The blast crisis phase diagnostic is based on the following criteria:

- In hemogram and/or myelogram the blast cells number is above 20% of total nucleated cells number;
- Extramedullary proliferation of blast cells.

The blast crisis phase in peripheral blood is usually manifested by leukocytosis, increased basophils and eosinophils number, normochromal anemia, thrombocytopenia. In cytochemical, morphological, immunological studies of blast cells the blast crisis type is defined: in 50% of patients the myeloid variant is diagnosed, 25% – lymphoblastic, 25% – undifferentiated variant. The bone marrow fibrosis presence is diagnosed in 50% of patients.

Clinically in CML blast crisis phase the *tumor intoxication syndrome* is observed – severe weakness, decrease in working capacity, intermittent fever to 38-39^{0}C, fever,

heavy sweats, significant weight loss; the *tumor proliferation syndrome* –bones and joints pain, heaviness and pain in the epigastric region, the left and right upper quadrant of the abdomen, hepatomegaly (liver extends at 15-20 sm below the costal arch), splenomegaly (spleen much enlarged, firm, sometimes occupies the whole left half of the abdomen), enlarged peripheral and mediastinal lymph nodes; *anemic syndrome* – skin paleness; *hemorrhagic syndrome* – petechiae, bruising, hemorrhage, bleeding.

Therapeutic tactics. According to the contemporary viewpoint, the first-line therapy in newly diagnosed CML is a tyrosine kinase inhibitor of the 1st generation – imatinib 400 mg daily per os, which is permanently assigned to as long as the patient is sensitive to the drug. Imatinib represents targeted therapy and in 96% of patients with CML achieved a complete hematological response. In the context of insensitivity to imatinib at standard dosage it is necessary to raise the dose up to 600-800 mg per day. If no effect the prescriptions of tyrosine kinase inhibitors of the 2nd generation (dasatinib, nilotinib) can be considered. The hydroxycarbamide (hydroxyurea), anagrelid or interferon assignment as the first-line therapy should be used in elderly patients and patients who have contraindications for the imatinib treatment.

In the blast crisis phase patients taking imatinib should increase its dose up to 600-800 mg per day. With the ability the 2nd generation of tyrosine kinase inhibitors is prescribed or the transplantation is recommended. The treatment of blast crisis is held by PCT assignment as needed depending on the blasts variant (myeloblastic or lymphoblastic).

Prognosis. CML belongs to chronic diseases; in case of the application of modern treatment methods the recovery is possible; in blast crisis phase – unfavorable prognosis.

Polycytemia Vera (PV)

PV is a clonal disorder involving a multipotent hematopoietic progenitor cell in which phenotypically normal red cells, granulocytes, and platelets accumulate in the absence of a recognizable physiologic stimulus.

2016 World Health Organization diagnostic criteria for polycythemia vera	
Major criteria	
1.	Hemoglobin > 16.5 g/dL(men) Hemoglobin > 16.0 g/dL (women) or Hematocrit > 49% (men) Hematocrit > 48% (women) or increased red cell mass more than 25% above mean normal predicted value
2.	BM biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)
3.	Presence of JAK2 or JAK2 exon 12 mutation
Minor criteria	
1.	Subnormal serum erythropoietin level

Clinical features. Isolated thrombocytosis, leukocytosis, or splenomegaly may be the initial presenting manifestation of PV.

Uncontrolled erythrocytosis causes hyperviscosity, leading to neurologic symptoms such as vertigo, tinnitus, headache, visual disturbances, and transient ischemic attacks (TIAs). Systolic hypertension is also a feature of the red cell mass elevation. In some patients, venous or arterial thrombosis may be the presenting manifestation of PV. Any vessel can be affected; but cerebral, cardiac, or mesenteric vessels are most commonly involved. Intraabdominal venous thrombosis is particularly common in young women and may be catastrophic if a sudden and complete obstruction of the hepatic vein occurs.

Treatment. The goals of treatment are to reduce complications and therefore improve survival.

Phlebotomy serves initially to reduce hyperviscosity by bringing the red cell mass into the normal range while further expanding the plasma volume. Periodic phlebotomies thereafter serve to maintain the red cell mass within the normal range and to induce a state of iron deficiency that prevents an accelerated reexpansion of the red cell mass. In most PV patients, once an iron-deficient state is achieved, phlebotomy is usually only required at 3-month intervals.

Aspinin 100 mg daily per os decreases the risk of thrombotic events and death from cardiovascular causes.

High-risk patients should be considered for cytoreductive therapy. Hydroxycarbamide (HC) is a cytoreductive agent. HC has a dose-dependent effect and needs to be individually titrated to achieve optimal count control. The efficacy of HC in controlling blood counts and preventing thrombosis. Primary dose is 500-1000 mg daily per os. Interferon (IFN-α) can be successfully used to normalise blood counts, reduce splenomegaly and prevent thrombosis in PV. It is also effective in many patients in reducing pruritus.

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.

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 incrases, which without treatment over time can reach huge numbers (500-1000×10^9/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 spleenomegaly 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 >5.0x10^9/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 normocellucal, 30% of all nuclear cells – mature lymphocytes.

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

- absolute lymphocytosis in peripheral blood ≥5.0x10^9/ 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) (κ/λ > 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.

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 (>5.0x10^9/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 <100×10^9/L); there can be organomegaly and anemia.	High	1,5-2

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

Stage	Clinical features	Risk group	Average survival, years
A	Hemoglobin > 100 g/L, platelets> 100x10^9/L; less than 3 lymph areas are injured.	Low	> 9
B	Hemoglobin > 100 g/L, platelets> 100x10^9/L; more than 3 lymph areas are injured.	Middle	5
C	Hemoglobin <100 g/L and/or platelets <100×10^9/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 lavoratory 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 38^0C 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.

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

The chemotherapy schemes often used in CLL treatment:

1. COP: vincristine 1.4 mg/m^2 intravenous the 1st day, cyclophosphamide 400 mg/m^2 i/v during 1-5 days, prednisone 40 mg/m^2 per os 1-5 days every 3 weeks.

2. FC: fludarabine 25-30 mg/m^2 intravenous during 1-3 days, cyclophosphamide 250-300 mg/m^2 intravenous 1-3 days every 4 weeks.

3. FCR: fludarabine 25 mg/m^2 intravenous 1-3 days, cyclophosphamide 250 mg/m^2 intravenous 1-3 days, rituximab 500 mg/m^2 intravenous on the 1st day (the 1st course the rituximab dose is 375 mg/m^2) every 4 weeks.

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. Specify the most characteristic changes in the peripheral blood of chronic phase chronic myeloid leukemia?

A. Leukocytosis with granulocyte shift and basophilic-eosinophilic association
B. Anemia
C. Lymphocytosis
D. Reticulocytosis
E. Thrombocytopenia

3. What changes of peripheral blood are pathognomonic for chronic lymphocytic leukemia?

A. Absolute lymphocytosis
B. Leukopenia
C. Eosinophilia

D. Lymphocytopenia
E. Leukocytosis with a shift of granulocyte

4. Cytogenetic sign of chronic myeloid leukemia is:
A. Philadelphia chromosome
B. Translocation of chromosome 7
C. XXX or XXY combination
D. Translocation of chromosome 19
E. Deletion of chromosome 13

5. One of the major diagnostic criterias for polycythemia vera is:
A. Presence of JAK2 or JAK2 exon 12 mutation
B. Thrombocytopenia
C. Philadelphia chromosome
D. BCR/ABL gene mutation
E. None of the above

6. Acute or chronic leukemia variant is determined by:
A. Type of progenitor cells of the tumor clone (substrate)
B. Nature of onset of the disease (rapid, progressive)
C. The nature and duration of disease flow
D. Efficacy or resistance to cytotoxic therapy
E. Features of clinical symptoms

7. Chronic myelogenous leukemia - is a malignant neoplasm of the hematopoietic system, arising from:
A. Cell myelopoiesis early predecessors, differentiated to mature forms
B. Cell myelopoiesis early predecessors, not differented to mature forms
C. Pluripotent hematopoietic cells incapable of maturing
D. Bone marrow cells with early development of myelofibrosis
E. Cell myelopoiesis predecessors, retain the ability to differentiate into mature forms with a predominance of proliferation of erythroid marrow

8. 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

9. The Philadelphia chromosome is at cytogenetic analysis of bone marrow cells that is present in case of:
A. Chronic myelogenous leukemia
B. Erythremia
C. Acute myeloid leukemia
D. Plasmacytoma
E. Lymphogranulomatosis

10. The terminal phase (blast crisis) of chronic myeloleukemia is characterized by:
A. All of the list
B. Generalization of tumor
C. Anemia and thrombocytopenia
D. Polyclonal tumor proliferation
E. Refractory to cytostatics

Real-life situations to be solved:

1. 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 – $3.5x10^{12}$/l, Hb – 98 g/l, the color index – 0.8; MCV - 95,8 fl, platelets – $96x10^{9}$/l, white blood cells $318.0x10^{9}$/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?

2. The patient is 49 years old, complains of pain in the left upper abdomen, general weakness, fatigue, weight loss. Objectively: skin and mucous membranes moderately pale, clean, peripheral lymph nodes were not enlarged. Pulse -. 92 / min, rhythmic. Liver + 4 cm, painless, dense, the lower edge of the spleen +10 cm. In blood test: HGB - 90 g/l, erythrocytes - $3,0x10^{12}$/L, color index - 0.9, leukocytes - $140,0x10^{9}$/l, promyelocytes - 10%, myelocytes - 13%, metamyelocytes - 11%, bands -28%, segments - 22%, eosinophils - 5%, basophils - 4% lymphocytes - 4% monocytes - 3%, platelets - $345,0x10^{9}$/l. ESR -38 mm/h. What is the most likely diagnosis?

Recommended literature:

I. Main:

1. Internal Medicine: in 2 books. Book 1. Diseases of the Cardiovascular and Respiratory Systems: textbook / N.M. Seredyuk, I.P. Vakaliuk, R.I. Yatsyshyn et al. Київ, Медицина., 2019. - 664 + 48 кольор. вкл.).
2. Internal medicine: Part 1 (cardiology, rheumatology, haematology): textbook for English-speaking students of higher medical schools / edited by Professor M.A. Stanislavchuk and Professor V.A. Serkova. - Vinnytsia: Nova Knyha, 2019. - 392 p.

3. Медицина за Девідсоном: принципи і практика / Навчальний посібник: пер. 23-го англ. вид.: у3 т. Т.3 С. Ралстона, Я. Пенмана, М. Стрекена, Р. Гобсона; К.: ВСВ «Медицина», 2021. – 642 с.
4. CURRENT Medical Diagnosis and Treatment 2012, Fifty-First Edition (LANGE CURRENT Series) by Stephen McPhee, Maxine Papadakis and Michael W. Rabow (Paperback - Sep 12, 2011)/
5. Побічнадіяліків – SideEffectsofMedications: навчальнийпосібнику 2 т. / зазаг.ред. В.М. Бобирьова, М.М. Потяженка. – Вінниця:
6. Cardiovascular diseases. Classification, standards of diagnosis and treatment / Edited by Academician Kovalenko V.M., Prof. Lutaia M.I., Prof. Sirenko Yu.M., Prof. Sychova O.S. – Kyiv. – 2020.
7. Perederii V.H., Tkach S.M. Principles of internal medicine. – Vol.2 / Textbook for students of higher educational institutions. – Vinnytsia: Nova knyha. – 2018.
8. Internal diseases. The textbook based on the principles of evidentiary medicine, 2018.

II. Additional literature:

1. Recommendations of the Association of Cardiologists of Ukraine for the diagnosis and treatment of chronic heart failure / Voronkov L.H. – moderator, working group of the Ukrainian Association of Heart Failure Specialists. – 2017.
2. Respiratory diseases / Ghanei M. - In Tech, 2012. - 242 p.
3. Clinical respiratory medicine / Spiro S., Silvestri G., Agusti A. - Saunders, 2012. - 1000 p.
4. Principles and practice of interventional pulmonology / Ernst A., Herth F. - Springer, 2012. - 757 p.
5. Clinical respiratory medicine / Spiro S., Silvestri G., Agusti A. - Saunders, 2012. - 1000 p.
6. Petrov Y. The chief symptoms and syndromes in patients with cardiovascular pathology : The practical handbook fur medical students / Ye. Petrov, Yu. Goldenberg, N. Chekalina; UMSA. - Poltava : TexcepBic, 2010. - 143.

7. Gastroenterology and Hepatology Board Review: Pearls of Wisdom, Third Edition (Pearls of Wisdom Medicine) by John K. DiBaise (May 11, 2012)
8. Clinical Pulmonology 2012 (The Clinical Medicine Series) by M.D., C. G. Weber (Oct 30, 2011) - Kindle eBook
9. Clinical Nephrology 2012 (The Clinical Medicine Series) by M.D., C. G. Weber (Sep 19, 2011) - Kindle eBook
10. Clinical Nephrology 2012 (The Clinical Medicine Series) by M.D., C. G. Weber (Sep 19, 2011) - Kindle eBook
11. Hematology: Clinical Principles and Applications, 4e by Bernadette F. Rodak MS MLS (Feb 18, 2017)
12. Rheumatology, 2-Volume Set: EXPERT CONSULT - ENHANCED ONLINE FEATURES AND PRINT, 5e by Marc C. Hochberg MD MPH, Alan J. Silman MD, Josef S. Smolen MD and Michael E. Weinblatt MD (Oct 19, 2019)
13. Endocrine Pathology: Differential Diagnosis and Molecular Advances by Ricardo V. Lloyd (Nov 5, 2018)
14. Clinical Endocrinology 2012 (The Clinical Medicine Series) by M.D., C. G. Weber (Sep 19, 2017) - Kindle eBook
15. Williams Textbook of Endocrinology: Expert Consult-Online and Print, 12e by Shlomo Melmed, Kenneth S. Polonsky MD, P. Reed MD Larsen and Henry M. Kronenberg MD (May 27, 2016)
16. Electrocardiography, 3e with Student CD (Booth, Electrocardiography for Health Care Personnel) by Kathryn A. Booth (Jan 27, 2017)
17. Echocardiography Review Guide: Companion to the Textbook of Clinical Echocardiography: Expert Consult: Online and Print, 2e (Expert Consult Title: Online + Print) by Catherine M. Otto (Mar 7, 2017).

Composed by **Lymanets T.V.**