

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

"Approved"

at the meeting of internal
medicine №1 department

Head of Department

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

<i>Academic discipline</i>	Internal medicine
<i>Module</i>	Basics of Internal Medicine
<i>Content module</i>	Fundamentals of diagnostics, treatment and prevention of hematological diseases
<i>Study subject</i>	Chronic leukemias
<i>Course</i>	IV
<i>Faculty</i>	Of foreign students training

The subject of the lesson: Chronic leukemias

The 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. At the age of 20 years CML is rare. Men suffer more women.

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. Aetiology and pathogenesis of CLL and CML.
2. Clinical symptoms of CLL and CML.
3. Modern classification of CLL and CML.
4. Methods of diagnostics of CLL and CML.
5. Methods of treatment of CLL and CML.

The student must be able:

1. To choose the symptoms of CLL and CML from the history data.
2. In examination of the patient to choose the symptoms of CLL and CML.
3. To make the scheme of investigation for the determination CLL and CML.
4. To define the cause and the severity of CLL and CML.
5. To assess the haemologic study results.
6. To determinate the treatment of patients with CLL 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 and CML.

The main problems of the lesson:

1. CLL and CML, definition, aetiology & pathogenesis.
2. Classification of CLL and CML: pathogenetic classification, morphogenetic classification, international classification.
3. Clinical manifestations of CLL and CML: clinical syndromes.
4. Targeting 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 22th 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 $800 \times 10^9/L$), 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 $400-800 \times 10^9/L$ 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-erythroblast ratio is more than 10:1, in 40-50% megakaryocytosis 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 (2008):

- Increasing the number of leukocytes, myelocytes, metamyelocytes, promyelocytes;

- 10-29% blast cells in the hemogram and / or myelogram;

- Progressive thrombocytosis (resistant to treatment), sometimes up to $1500-2000 \times 10^9/L$ or progressive thrombocytopenia $<100,0 \times 10^9/L$, 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 patient's 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 38-39⁰C, 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 (Gleevec) 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.

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 ($sIgD \pm sIgM$).

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	Middle	5

	injured.		
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 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°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/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 $25\text{-}30 \text{ mg/m}^2$ intravenous or 40 mg/m^2 per os during 1-3 days, cyclophosphamide $250\text{-}300 \text{ mg/m}^2$ intravenous 1-3 days every 4 weeks.
3. FCR: fludarabine 25 mg/m^2 intravenous or 40 mg/m^2 per os 1-3 days, cyclophosphamide 250 mg/m^2 intravenous 1-3 days, rituximab 500 mg/m^2 intravenous drip 1st day (the 1st course the rituximab dose is 375 mg/m^2) every 4 weeks.
4. CFAR: cyclophosphamide 250 mg/m^2 IV during 3-5 days, fludarabine 25 mg/m^2 IV or 40 mg/m^2 per os 3-5 days, alemtuzumab 30 mg IV drip ($\geq 2 \text{ h}$) 1, 3, 5 days, rituximab 375 mg/m^2 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 ($> 50 \times 10^9/\text{L}$), 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. 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. The 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. Hairy Cell Leukemia refers to tumors of the predecessors:

- A. B-cell
- B. T-cells
- C. Myeloid cells
- D. Macrophages
- 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 differentiated 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 – $3.5 \times 10^{12}/l$, 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?

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 - $3,0 \times 10^{12}/L$, color index - 0.9, leukocytes - $140,0 \times 10^9/l$, promyelocytes - 10%, myelocytes - 13%, metamyelocytes - 11%, bands -28%, segments - 22%, eosinophils - 5%, basophils - 4% lymphocytes - 4% monocytes - 3%, platelets - $345,0 \times 10^9/l$. ESR -38 mm/h. 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.Loffler, J.Rastetter, T.Haferlach. 6th edition. Atlas of clinical hematology. Springer Berlin Heidelberg New York, 2006. – 429 p.

2. Chronic Lymphocytic Leukemia / edited by Susan O'Brien, John G. Gribben. – CRC Press, 2008. – 312 p.
3. Chronic Myeloid Leukemia: New Insights for the Healthcare Professional: 2013 Edition / by Q. Ashton Acton. – ScholarlyEditions, 2013. – 124 p.

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