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Guidelines for conducting a practical lesson with 5th year students of the Faculty of Medicine on the topic:

ACUTE LEUKEMIA

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Guidelines for conducting a practical lesson with 6th year students of the Faculty of Medicine on the topic:

Acute leukemia is a severe fatal disease of the blood system, refers to hemoblastoses. It has been established that when clinical syndromes or individual symptoms develop, the disease practically enters its last stage. It can begin and proceed under the guise of many other diseases of a therapeutic and non-therapeutic profile. This should be constantly remembered. Much of the early diagnosis can be decided by a routine blood test and specialist consultation.

This methodological development contains information mainly on differential diagnosis, the main criteria for the disease, i.e. what a general medical doctor needs. In this regard, the main purpose of this manual is to introduce students to this pathology and to obtain the necessary practical skills and abilities for the diagnosis and differential diagnosis of acute leukemia.

MAIN ISSUES COVERED IN THE DEVELOPMENT:

1. Brief information about the etiology and pathogenesis of AL.

2. Modern classification of OL.

3. Main clinical syndromes in patients with AL, their characteristics and mechanisms of development.

4. Stages of the course of OL and their characteristics.

5. Reference criteria for the diagnosis of OL.

6. Differential diagnosis of OL with chronic leukemia, aplastic anemia, cancer metastases to the bone marrow.

7. Basic principles of treatment of patients with OL. Modern approaches to the appointment of polychemotherapy.

BLOCK OF INFORMATION AND GUIDELINES

Definition of acute leukemia, etiology, pathogenesis. Leukemia is a group of tumors arising from hematopoietic cells (hemoblastosis), usually affecting the bone marrow. The nature of leukemias has not yet been precisely established. The provoking role of some chemical mutagenic (leukosogenic) substances (benzene) and ionizing radiation can be considered proven. In the etiology of "spontaneous" leukemia in humans, not caused by any external influence, its viral etiology is assumed. This refers to an endogenous virus that intrudes into a cellular gene and introduces the corresponding genetic information, i.e. programming the development of ancestral stem cells according to the blast and leukemic type. In favor of the possible viral nature of leukemia, the facts of the so-called horizontal spread of leukemia in individual families, when non-relatives fall ill with leukemia, are given. The significance of the genetic factor in the development of leukemia is confirmed by cases of the same form of leukemia in relatives, in particular, in identical twins.

The basis of the modern view on the pathogenesis of leukemia is the clonal theory of the origin of leukemia (Vorobiev A.I.; 1979), according to which leukemia is based not on a perversion of the activity of the entire hematopoietic system, not on a violation of the maturation of healthy cells, but on the appearance of one mutated cell at the beginning , and then from it many tumor cells, i.e. clone of leukemic cells. They carry the same changes as the original mutated cell.

Depending on the severity of the tumor progression of the formed clone of cells, hemoblastoses are conditionally divided into "malignant" and "benign". OLs are among the first of them.

Thus, the secret morphological substrate of OL is the blast cell, which can produce its offspring if, at the same time, there is a weakening of the immune mechanisms that are unable to destroy or recognize the leukemic cell.

Classification and clinical and hematological forms of acute leukemia, complications. Acute leukemias are malignant tumors, the substrate of which is young (blast) blood cells. Depending on the type of blasts (myeloblasts, lymphoblasts, monoblasts, erythroblasts and undifferentiated blasts), which represent leukemic cells, acute leukemias are divided into the corresponding forms. The leukemic clone of cells has the ability to suppress normal hematopoiesis, causing anemia and thrombocytopenia.

The main criterion for the diagnosis of acute leukemia is the appearance in the peripheral blood of the youngest (blast) cells that can predominate in the leukogram. Intermediate cells are almost never detected, there is a small number of mature leukocytes. This ratio of cells is called "leukemic gaping". Blastosis of peripheral blood can be both against the background of a sharply increased, and normal or reduced number of leukocytes.

According to the classification of Vorobyov I.A. et al. (1979) and in accordance with the WHO recommendation, acute leukemias are distinguished:

1. Acute myeloid leukemia.

2. Acute monoblastic (myelomonoblastic) leukemia.

3. Acute erythromyelosis (erythroleukemia).

4. Acute megakaryoblastic leukemia

5. Acute promyelocytic leukemia.

6. Acute lymphoblastic leukemia in children (under 20 years old)

7. Acute lymphoblastic leukemia in adults.

8. Acute plasmablastic leukemia.

9. A low percentage form of acute leukemia.

10. Acute undifferentiated leukemia.

Currently, the stages of the disease are distinguished:

1. the first attack (the height of the disease);

2. remission (complete or partial);

3. recovery (a state of complete clinical and hematological remission, lasting at least 5 years);

4. recurrence (what number, clarification of the focus in case of local recurrence);

5. terminal stage

Abroad, the so-called FAB classification (France, England, America 1976 - 1980) has been adopted, according to which leukemias are divided into two large groups:

1. acute lymphoblastic leukemia (ALL),

2. acute non-lymphoblastic leukemia (ONLL).

ALL are subdivided into:

L-1 - ALL with a predominance of small, lymphoid cells without immunological markers. It occurs in 85% of children and 5-10% in adults.

L-2 - ALL with typical lymphoblasts. It occurs more often in adults.

L-3 - Acute macro- or prolymphocytic leukemia with a predominance of very large blast cells.

ONLL are divided into:

M-0 - acute undifferentiated leukemia.

M-1 - AML without cell maturation.

M-3 - acute promyelocytic leukemia.

M-4 - acute myelomonoblastic leukemia.

M-5 - acute monoblastic leukemia.

M-6 - acute erythromyelosis.

M-7 - acute megakaryoblastic leukemia.

Preleukemia - myelodysplastic syndrome (refractory anemia, sideroblastic anemia, refractory anemia with an excess of blast cells) transforms into ONLL in 40-60% of cases.

ALL subtypes:

• acute T-blast leukemia;

• acute B-blast leukemia;

• acute O-blast leukemia.

CLINIC OF VARIOUS OPTIONS OF ACUTE LEUKEMIA.

There is no typical clinical picture of acute leukemia, the undoubted signs of acute leukemia in the blood and bone marrow are not always manifested by clinical signs. The disease is often detected during clinical examination or examination of the patient for another disease. The diagnosis of acute leukemia is established only morphologically - by identifying the youngest (blast) cells in the blood or bone marrow.

The following clinical syndromes can be distinguished in the advanced stage of OL: anemic, toxic-septic, ulcerative-necrotic (oral), hemorrhagic, hyperplastic, hematological, extramedullary manifestations.

All these syndromes are due to the suppression of normal hematopoiesis, the development of immunological defenselessness, and metastasis of hemoblastosis to other organs and systems.

Low percentage acute leukemia. Low-percentage acute leukemia is characterized by a low content of blast cells in the blood (<10-20%) and a lower content of blastosis in the bone marrow, which is difficult to diagnose. It is rare, mostly in the elderly.

Acute myeloid and myelomonoblastic leukemias. These types of leukemias are common, the average age of patients with acute myeloid leukemia is 38 years, with myelomonoblastic leukemia - 50 years. The disease is manifested by hematological disorders. Severe onset of the disease with high fever, necrosis in the throat is typical for cases with primary granulocytopenia (below 750-500 granulocytes per microliter of blood). Children often have extramedullary lesions (liver, spleen, neuroleukemia). Extramedullary manifestations in adults indicate a late stage of progression.

The recurrence of acute myeloid leukemia is characterized by various signs: either against the background of successful maintenance therapy, cytopenia increases and blast cells appear, or extramedullary growth foci appear. In this regard, patients with acute leukemia in remission are under the control of a hematologist with a mandatory blood test at least once every 1-3 months.

Patients die from deep oppression of hematopoiesis, when the process spreads to other organs - from disorders incompatible with life and septicemia. The blood picture is typical for acute leukemia (anemia of various types, leukocytosis or leukopenia with blasts, thrombocytopenia).

The frequency of remissions in acute myeloblastic and myelomonoblastic acute leukemia is about 50%, life expectancy is 6-12 months, with achieved remission - 1.5-2 years (Kovaleva LG, 1990).

Acute promyelocytic leukemia. This form of leukemia was isolated as an independent form in 1957 due to the outward resemblance of tumor cells to promyelocytes. A feature of acute promyelocytic leukemia is the severity of the hemorrhagic syndrome, which can precede the clinical picture of leukemia for several months; symptoms of intoxication, weakness, sweating increase slowly. Blast cells in the bone marrow are 75-85%, infiltration of tubular bones by blasts is often absent, there is no enlargement of lymph nodes, the liver and spleen rarely increase, the blood picture is characterized by polymorphism of blast cells.

The course is malignant. Thanks to the use of rubomycin, the average life expectancy of patients who have achieved remission has lengthened to 26 months, and sometimes up to 3 or more years.

Acute monoblastic leukemia. Acute monoblastic leukemia occurs in adults in 6.3%, and in children - in 2.6% of cases. The clinic is similar to myeloid leukemia, necrosis in the oral cavity associated with neutropenia is more common. The process is localized in the bone marrow, often develops infiltration of the skin, gums, in the later stages - in all internal organs.

The blood picture in monoblastic leukemia is characterized by a feature of blast cells: blast cells are large with a bean-shaped nucleus and several nucleoli, the cytoplasm is smaller than that of a monocyte, but more than that of a myelocyte, its color is from gray-blue to blue. The course of an acute monoblastic leukemia is malignant, the average life expectancy is 5-12 months.

Acute erythromyelosis. Acute erythromyelosis was first described in 1917, occurs in patients with a history of radiation or chemotherapy, more often in patients with lymphogranulomatosis, multiple myeloma and erythremia. In acute erythromyelosis, anemia (moderately hyperchromic) is characteristic from the very beginning, sometimes they appear later.

The picture of blood and bone marrow is characterized by a sharp increase in the cells of the red germ, it is similar to the picture of blood in hemolytic anemia and pernicious anemia. Unlike other leukemias, red cells often differentiate to a normocyte or erythrocyte. Along with the cells of the red germ, blast cells later appear in the blood. Until an accurate diagnosis is established, treatment with cytostatics and prednisolone should not be carried out. The average life expectancy is about 6 months, and 20% of patients live 12 months.

Acute lymphocytic leukemia. Acute lymphocytic leukemia predominates in childhood (2-4 years), in adults it occurs in 10-15% of patients.

The peculiarity of the clinical picture is an increase in lymph nodes (54%), spleen (71%). pain in the legs (ossalgia). The blood picture is characteristic of acute leukemia. Extramedullary metastases in acute lymphoblastic leukemia have a better prognosis than in myeloblastic leukemia.

The frequency of remissions in children is 94%, in persons older than 15 years - 50%. The frequency of recovery in children is more than 50%.

Acute plasmablastic leukemia. A feature of this form is the ability of the cells that form it to produce pathological immunoglobulins. Plasma acute leukemia is represented in the bone marrow and blood mainly by plasmablasts. This leukemia proceeds with the suppression of normal hematopoietic sprouts, sometimes with extramedullary foci of leukemic growth. The clinical course does not differ from other forms of leukemia.

Acute megakaryoblastny leukemia. It is rare, diagnosed morphologically. Characteristic for acute megakaryoblastic leukemia is the presence in the blood and bone marrow, along with blast cells, megakaryoblasts. Often there are malformed megakaryocytes, fragments of the nuclei of megakaryocytes, accumulations of platelets. The clinical picture has no characteristic features.

DIFFERENTIAL DIAGNOSIS. In the differential diagnosis of acute leukemia with aplastic anemia, it should be noted that aplastic anemia is characterized by normochromic anemia, a decrease or absence of reticulocytes in the peripheral blood, leukopenia, granular and thrombocytopenia. The diagnosis of the latter is reliable in the study of the bone marrow by trepanobiopsy of the iliac wing; a significant increase in fat, a decrease in the cellular composition, the disappearance of mega- and erythrokaryocytes. Acute leukemia is characterized by the detection of blast tumor cells in the blood and bone marrow.

Acute leukemia should be differentiated from infectious mononucleosis, the main symptoms of which are fever, tonsillitis and lymphadenopathy; sometimes there is hemorrhagic diathesis. In the blood, leukocytosis (10000-30000) is neutrophilic. As the disease progresses, the predominance of lymphocytes (60-70%), monocytes (15-30%) increases. Characteristic of mononucleosis is the presence of peculiar cells of lymphomonocytes, atypical monocytic cells and plasma cells (5-15%), red blood, the number of platelets is normal, there are no deviations from the norm in the bone marrow punctate. Acute leukemia is characterized by progressive anemia and thrombocytopenia. The presence of blast forms in the peripheral blood and the absence of intermediate elements between them and mature leukocytes - "leukemic gaping" - are reliable for acute leukemia.

Acute promyelocytic leukemia, characterized by the severity of the hemorrhagic syndrome, should be differentiated from Werlhof's disease, the main symptoms of which are hemorrhages on the skin, mucous membranes and bleeding. On the part of the blood, thrombocytopenia with a sharp decrease in the number of platelets and an increase in megakaryocytes in the bone marrow, impaired retraction of the blood clot, prolongation of the bleeding time (up to 10-30 minutes or more), positive symptoms of "pinch" and "harness". To exclude acute leukemia, blood tests and bone marrow punctate are decisive.

Sometimes acute myeloid leukemia begins with the appearance in the blood of not only the youngest (blast) cells, but also intermediate and mature forms. For differential diagnosis with chronic myeloid leukemia, a cytogenetic study of blood or bone marrow is performed. In the terminal stage of chronic myeloid leukemia, a typical chromosomal defect is preserved - the so-called Philadelphia chromosome, which does not occur in acute leukemia.

In relation to the differentiation of acute leukemia with leukomoid reactions, the presence in the body of septic, inflammatory processes, pulmonary tuberculosis is important. Reactions of the myeloid type - granulocytic - are observed in septic conditions. occur with cell rejuvenation, but signs of infection are always expressed (fever, ESR, etc.) Leukemoid reactions in acute immune hemolysis are similar to acute erythromyelosis, hemolysis can complicate erythromyelosis; the presence of atypical erythrocaryocytes and a high percentage of blast cells make it possible to exclude leukemoid reactions and make a diagnosis of acute erythromyelosis. Leukemoid reactions of the monocytic type are found in tuberculosis, sarcomas, rheumatism, chronic pyelonephritis, where the picture of the disease is pronounced, in doubtful cases, trephine biopsy of the bone marrow is indicated.

Acute consumption thrombocytopenia (with lobar pneumonia) is sometimes mistakenly regarded as the aleukemic stage of acute leukemia, the absence of blasts in the bone marrow points is decisive for the exclusion of acute leukemia.

PRINCIPLES OF TREATMENT OF ACUTE LEUKEMIA. The main task of the treatment of acute leukemia is to eradicate leukemic cells and obtain a long-term continuous remission, bordering on recovery. If it is not possible to achieve remission, then the therapeutic tactics fundamentally change and therapy for the containment of tumor growth begins.

Therapy of acute leukemia is based on several principles. Firstly, a differentiated approach to the treatment of various forms of acute leukemia is used, which are isolated depending on the belonging of leukemia cells to a particular hematopoietic lineage.

Secondly, the treatment of acute leukemia is carried out according to programs that include not only the stage of achieving remission, but also treatment in remission, aimed at destroying the remnants of tumor cells. At the same time, the program for the treatment of acute lymphoblastic and undifferentiated forms of leukemia in children is based on the effectiveness of the continuous use of cytostatics with low toxicity to normal tissues. However, the program for the course of acute lymphoblastic and undifferentiated leukemias in adults requires intensification at the stage of treatment during remission, which is supported by complex combinations of cytostatic drugs that replace each other, otherwise a relapse occurs. In the treatment of non-lymphoblastic leukemia, starting from the period of remission induction, intensive course cytostatic therapy is used, which is quite toxic for normal hematopoiesis, it determines both the frequency of achieving remission and its duration.

Differentiation of the forms of acute leukemia is, first of all, cytochemical and only partly morphological. For accurate identification of forms, it is necessary to use the entire spectrum of cytochemical reactions. Checking only the activity of peroxidase in blast cells does not allow isolating acute non-lymphoblastic leukemia with a negative reaction to peroxidase.

Orientation to clinical symptoms, for example, to an increase in lymph nodes and. spleen in determining the form of acute leukemia can lead to an erroneous assignment of a process of a monoblast or myelomonoblastic nature to a lymphoblastic one (both lymph nodes and the spleen can be enlarged), which, in turn, will lead to an erroneous choice of therapy.

In order to carry out a modern effective treatment program, it is necessary from the first day of therapy to place a patient in leukemic neutropenia or agranulocytosis in aseptic conditions, at least to isolate the patient and use ultraviolet lamps shielded from him in the ward. To prevent necrotizing enteropathy, such a patient should be prescribed non-absorbable antibiotics, such as biseptol (up to 6 tablets per day) with nystatin (4-6 million units per day).

After a course of cytostatic therapy, when intoxication increases due to increased cellular decay, DIC and respiratory failure often occur, it is advisable to inject a large amount of fluid into the patient: saline solutions, reopoliglyukin, fresh frozen plasma. During this period, plasmapheresis can be carried out for prophylactic purposes. With the development of such complications, plasmapheresis becomes a necessary way to eliminate them.

In the case of initial cytopenia: with a level of leukocytes less than 2000, platelets less than 30,000, the doses of cytostatic drugs should be halved.

There is no generally accepted setting for the duration of program treatment for various forms of acute leukemia.

However, it is believed that, on average, the patient should be actively treated for at least 5 years.

For the treatment of acute leukemia, various combinations (schemes) of cytostatics are used.

The following combinations of cytostatic drugs are most effective:

1. VAMP

• V-vincristine, 2 mg/m2 on the 2nd day of the course intravenously (1 time per week).

• A-methotrexate (ametopterin), 20 mg/m2 on the 1st and 4th day of the course intravenously.

• M-6 mercaptopurine 60 mg/m2 daily for 8 days.

• P-prednisolone, 40 mg/m" daily for 8 days (prednisolone cancel immediately).

2. COAP

• P-cyclophosphamide, 50 mg/m2 3 times a day, intravenously for 4 days in a row.

- O-vincristine (ONKOVIN), 2 mg 1 time per course of treatment intravenously.

- A-cytosine - arabinoside, 50 mg/m2 3 times a day intravenously drip for 2 hours.

- P-prednisolone, 60-200 mg orally for 4 days in a row.

3. Cytosar + rubomycin,

a) "7+3" combination: Cytosar - 100 mg/m2, intravenously for 7 days; rubomycin, 45 mg/m2 intravenously on the first 3 days of the course.

b) "5+2": cytosar, 100 mg/m2 5 days intravenously, rubomycin, 100 mg/m2 2 days (simultaneously with cytosar or after it for 6-7 days).

Treatment is carried out in courses of 4-8 days with an interval of 9-14 days. Compliance with the intervals reduces toxicity and allows the use of full courses of therapy. In the presence of cytopenia, minimal therapy is carried out, prevention and treatment of infectious hemorrhagic complications of hemoblastoses has been developed: isolation of patients and the creation of aseptic conditions for them (boxes, ultraviolet air sterilization, the use of bacterial solutions for personnel). Apply symptomatic agents, blood transfusions of erythrocyte and platelet mass 1-2 times a week. In the treatment of acute leukemia in the elderly (low-percentage form), a sparing tactic of therapy is recommended, according to indications, erythrocyte mass is prescribed, moderate doses of steroid and anabolic hormones. In the treatment of: acute promyelocytic leukemia, rubomycin and cytosar are used;

1. Heparin, 1 mg/kg 24 hours (together with platelet transfusion);

2. Epsilon-aminocaproic acid;

3. Kontrykal or trasilol, 50,000-100,000 IU per day;

4. Transfusion of platelet mass;

To maintain remission in all forms of leukemia, the same combinations (VAMP, COAP or "7 + 3") are used, with the help of which remission was achieved. Intervals of 9-19 days, control punctures of the bone marrow - 1 time in 1-3 months.

Treatment of relapses is carried out with the help of new cytostatics and their combinations.

Physio-, electro- and thermal procedures are contraindicated.

Sanatorium treatment - in the climate familiar to the patient (outside the period of cytopenia) is not contraindicated.

FORECAST, DISPENSERIZATION, EMPLOYMENT. The prognosis is unfavorable. Ability to work depends on the form, period of illness and the nature of the therapy.

Outside the period of cytopenia, patients can (if they strive for this) continue to work (without hypothermia, insolation and physical exertion). Patients with acute leukemia are assigned II and I groups of disability. Medical examination is carried out by a hematologist or therapist (visiting a hematologist 2 times a month) with consultations of related specialists (dentist, laryngologist, surgeon) at least 1-2 times a year. A hematologist performs maintenance therapy (mainly on an outpatient basis), blood control at least 2 times a month.