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Algorithm for the diagnosis of acute leukemia

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Abstract. Although the clinical picture of advanced acute leukemia is outlined quite clearly, there are practically no clinical symptoms that are specific, pathognomonic only for this disease. Therefore, even such seemingly specific manifestations of hematological diseases as hemorrhagic syndrome, anemia, enlargement of lymph nodes, liver and spleen, allows the doctor only to suspect acute leukemia and urgently refer the patient to a blood test. The identification of the process, the diagnosis of the disease can be carried out using only morphological methods.

Keywords: Acute leukemia, blast cell, cytochemistry, cytogenetics.

Introduction. Acute leukemias are a group of tumor diseases of the blood system (hemoblastoses), which are characterized by primary damage to the bone marrow by tumor (blast) hematopoietic cells, displacing the normal elements of hematopoiesis (16,2)

Among hemoblastoses, acute leukemia (AL) is one of the first in terms of frequency of occurrence. The incidence of AL is 5-6 cases per 100,000 population per year, 6-7% of all malignant neoplasms. (8,7,13,16)

In adults, the ratio of myeloid and lymphoid leukemia is approximately 6:1, in childhood 80-90% of all AL are lymphoblastic forms, and after 40 years, the opposite ratio is observed: in 80% of patients with AL, the myeloid variant of the disease is diagnosed. The median age of patients with acute non-lymphoblastic leukemias is 60–65 years old, with acute lymphoblastic leukemias - 10 years. (5,13,16).

In accordance with the modern scheme of hematopoiesis, acute leukemias are divided into 2 large, main groups - lymphoblastic and non-lymphoblastic (myeloid); in each of these groups on different variants are distinguished on the basis of morphological, cytochemical and immunological characteristics of blast cells. (11,2).

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Acute myeloid leukemia (AML) is a group of acute leukemia arising from a cell - a precursor of myelopoiesis, differing in certain morphological, immunophenotypic and cytogenetic characteristics. About 10% of AMLs are erythroid or megakaryocytic, so the more correct term is “acute non-lymphoblastic leukemias”. (4,7,17)

Depending on the degree of differentiation (maturity) of leukemic cells (myeloblasts), the following AML variants are distinguished:

- Acute myeloid undifferentiated leukemia (M0 according to FAB) accounts for 5% of all AML. Cytochemically, cells cannot be attributed to any subtype; the diagnosis is made only by immunophenotyping. For this variant of leukemia, no characteristic chromosomal aberrations were found. The prognosis with standard treatment is poor.

- Acute myeloid leukemia (M1 according to FAB) without signs of cell maturation is 15% of all AML. With this option, the minimum degree of myeloid differentiation is determined.

- Acute myeloid leukemia with a sign of maturation (M2 according to FAB) accounts for 25% of all AML. In case of M2 - variant of AML with t (8; 21), splenomegaly and granulocytic sarcoma are found in 25% of patients.

- Acute promyelocytic leukemia (APL; M3 according to FAB), a clearly defined nosological form with very characteristic clinical and laboratory signs (typical morphology of tumor cells, severe hemorrhagic syndrome, disseminated intravascular coagulation syndrome, leukopenia and young age of patients), which sometimes make it possible to establish a diagnosis based only on on clinical symptoms. APL accounts for 10% of all myeloid leukemias. In 80% of patients at the time of diagnosis, gleb leukopenia is determined, in 15 - 20% of patients at the onset of the disease, hyperleukocytosis can be determined (median 80 - 90 x 10^9/l). In almost all cases of APL, t is present t(15;17), which is key for confirming the diagnosis of APL.

-Acute myelomonoblastic leukemia (M4 according to FAB) is diagnosed in 25 - 30% of AML patients. Frequent hepatosplenomegaly, lymphadenopathy, gingival hyperplasia, skin infiltration, often CNS damage, DIC syndrome. The most common

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cytogenetic abnormalities t (9; 11), trisomy 4, t (1; 7), translocations associated with 11q23.

- Acute monoblastic leukemia (M5 according to FAB), which accounts for 10% of all AML, is characterized by leukocytosis, estmedular lesions (infiltration of the gums, skin, hepatosplenomegaly, CNS involvement), disseminated intravascular coagulation syndrome. The prognosis for this variant of the disease is unfavorable.

- Acute erythroblastic leukemia (M6 according to FAB), diagnoses less than 5% of AML cases in adults; it accounts for 10-20% of secondary leukemia.

- Acute megakaryoblastic leukemia (M7 according to FAB) occurs in 1-3% of all AML cases; the proportion of this form is characterized by myelofibrosis and osteosclerosis. The diagnosis is established only by immunophenotyping. The prognosis for this option is unfavorable. (1,3,4,12,15)

One of the most difficult diagnostic variants of AML is myeloblastic AML with minimal differentiation. It was highlighted among the last by the authors of the FAB-classification. The difference between the M0 variant and ALL lies in the expression of myeloid (CD33, CD13) and the absence of lymphoid antigens, as well as the presence of a PIC-positive substance in diffuse rather than granular form. On blasts M0 in contrast to Ml blasts, the antigens CD11b and CD15 are absent. (9,14)

Acute non-lymphoblastic leukemias not included in the FAB classification.

Acute eosinophilic leukemia -is rarely an independent disease that has arisen for the first time. Eosinophilia in the bone marrow without eosinophilia in the blood is observed in acute myelomonocytic leukemia and is associated with pathology in the region of chromosome 16. Along with this, the existence of eosinophilic leukemia is recognized as an independent disease that has arisen for the first time, and the number of eosinophils in the bone marrow and blood ranges from 50 to 80%. A specific histochemical reaction in acute eosinophilic leukemia is the detection of cyanide-resistant peroxidase in blasts. Acute eosinophilic leukemia is rarely an independent disease that has arisen for the first time. Eosinophilia in the bone marrow without eosinophilia in the blood is observed in acute myelomonocytic leukemia and is associated with pathology in the region of chromosome 16. Along with this, the

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Acute hybrid leukemia - acute hybrid (mixed, two-line) is called leukemia, in which more than 10% of cells have lymphoid and myeloid markers. In some cases, intralinear hybrid forms of leukemia are observed, in which the power cells have two or more markers of the myeloid lineage, for example, erythroid, granulocytic, or megakaryocytic markers (11)

Basophilic leukemia -is a very rare form of acute non-lymphoblastic leukemia. With this variant of leukemia, the number of blasts and basophilic promyelocytes and myelocytes is increased in the peripheral blood and in the bone marrow. Translocation t(6;9) is very often observed. To distinguish between basophilic and neutrophilic promyelocytes, toluidine blue staining is used. Basophilic leukemia can be confused with promyelocytic leukemia, but basophilic leukemia is characterized by urticaria and high levels of histamine in the blood (2,13,11)

Acute mast cell leukemia -is a very rare form of non-lymphoblastic leukemia, characterized by the presence of a large number of mast cells in the bone marrow. Patients with mast cell leukemia complain of severe weakness, fever, weight loss, abdominal pain, nausea, vomiting, diarrhea, and itching. The characteristic signs of the disease are hepatomegaly, splenomegaly, lymphadenopathy. In the analysis of peripheral blood, anemia, thrombocytopenia, leukocytosis (the number of leukocytes ranges from 10 to 150 x 10^9/l) and a very large number of mast cells are detected. Mast cells originate from hematopoietic cells, have a common progenitor cell with basophils. Normally, mast cells are not detected in the peripheral blood, and only a few mast cells are found in the bone marrow. Mast cells are well stained with Sudan black, do not contain peroxidase and α-naphthyl esterase. The characteristic surface markers of obesity receptors cells and basophils are Fc (IgE, IgG), C (C3a, C3b,

C5a), H2 (for histamine). In the blood with mast cell leukemia, the content of histamine is high. It should be noted that a large number of mast cells in the bone the brain is also observed in chronic lymphoproliferative diseases (Waldenstrom's disease, chronic lymphocytic leukemia, lymphomas), idiopathic sideroblastic anemia, chronic diseases of the liver, kidneys, osteoporosis.

Biphenotypic leukemia - with translocation t (4;11) - acute biphenotypic leukemia with signs of lymphoid and monocytic leukemia is associated with a chromosomal abnormality - translocation t (4;11) (q21;q23) and can develop in both children and adults. This variant of leukemia is characterized by hepato- and splenomegaly. Leukemic blast cells express surface markers characteristic of B-lymphocyte precursors and monoblasts BA-2 (CD24), TdT, and OCM (CD11b). In this variant, there is a violation of the genes responsible for the synthesis of immunoglobulins, and the oncogene c-ets-l, which is responsible for the ability of the stem cell to differentiate along the pathway of lymphopoiesis or monocytopoiesis. The prognosis for biphenotypic leukemia is poor.

Acute hypolastic myeloid leukemia - this form can occur in approximately 10% of all cases of acute myeloid leukemia. It is characterized by pancytopenia, the absence of blasts in the peripheral blood, the normal size of the liver, spleen, and the absence of lymphadenopathy. Patients are usually over 50 years of age. The bone marrow of such patients can be called "hypocellular", but among the available cells, blasts account for 15 to 75%.

Acute myeloid leukemia with Philadelphia chromosome - in about 2% of cases of acute myeloid leukemia, Philadelphia chromosome t (9;22) (q34;q11) is determined in 10-100% of leukemic (blast) cells. In this case, blast cells have surface antigens characteristic of myeloid leukemia (1,13). There is a point of view that in this situation we are talking about a blast crisis in chronic myeloid leukemia. The following arguments support this point of view:

-blast crisis can be observed literally in a few days after diagnosis of chronic myeloid leukemia with Philadelphia chromosome; in some cases, with a blast crisis, blast cells have cytogenetic features characteristic of chronic myeloid leukemia;

- normal platelet count and intermigrating increase in the level of basophils;

-a long prodromal period in the form of weakness, weight loss and the appearance of symptoms of chronic myeloid leukemia, such as agranulocytosis, due to treatment with cytostatics;

-acute myeloid leukemia with the presence of the Philadelphia chromosome has a very poor prognosis like a blast crisis;

-in some patients, after the onset of remission, phenotype changes appear, similar to the chronic phase of chronic myeloid leukemia;

-break points on chromosome 22 in the region of the M-bcr-gene and the product fusions of BCR-ABL P210 genes are identical to classical chronic myeloid leukemia.

There is also an alternative point of view:

-in most cases of acute myeloid leukemia with the presence of the Philadelphia chromosome, there is a mosaic karyotype;

- the Philadelphia chromosome may appear later during diseases;

-the Philadelphia chromosome in these cases is not associated with a gap in the M-bcr gene region on chromosome 22.

In addition, situations are known where acute Ph-positive myeloid leukemia developed after oligoblastic leukemia with the absence of the Philadelphia chromosome. Some cases of acute Ph-positive myeloid leukemia are mixed in the nature of the blasts, myeloblasts and lymphoblasts are found in the bone marrow. There are probably two variants of acute myeloid leukemia with the Philadelphia chromosome: one with a break point in the M-bcr region of chromosome 22 with the formation of the P210 protein, which should be considered similar to the blast crisis in chronic myeloid leukemia, and the second with the production of the P190 protein by the oncogene (6,11,15)

Acute lymphoblastic leukemia is the most common tumor of hematopoietic tissue in children, accounting for 30% of all malignant tumors of childhood; the peak incidence of ALL occurs at the age of 3-4 years. (11,16)

FAB classification identifies 3 morphological types of acute lymphoblastic leukemia (LI, L2, L3) based on the assessment of the size of blasts, the shape of the nucleus, the number of nucleoli, the ratio of the size and severity of the cytoplasm. To identify the types of L1 and L2 lymphoblasts, use cytological criteria expressed in points (table 1) (окороков)

Assessment of cytological signs of lymphoblasts in points.

Cytological signs	Points
The nuclear-cytoplasmic ratio is high (the cytoplasm is> 20% the entire cell area) in more than 75% of cells	+1
Nuclear-cytoplasmic ratio is low in more than 25% of cells	-1
Nucleoli are absent or invisible in more than 75% of cells	+1
Nucleoli are present in more than 25% of cells	-1
The nuclear membrane is uneven in less than 25% of cells	0
The nuclear membrane is uneven in more than 25% of cells	-1
Large cells make up less than 50% of all cells (the diameter of large cells are 2 times or more larger than the diameter of small lymphocytes)	0
Large cells account for more than 50% of all cells	-1

If the sum of points is from 0 to + 2, the cell belongs to L1, if from 1 to 4 - to L2.

It should be noted that quite often group 2 lymphoblasts (L2) difficult to distinguish from myeloblasts in M0 and M1 variants of myeloid leukemia. In addition, in approximately 10% of cases of acute lymphoblastic leukemia, there are morphologically heterogeneous populations of lymphoblasts, one population consists of L1 blasts, the other - of L2 blasts. Distinguishing between L1 and L2 cells is important because it was proved that children with L1 acute lymphoblastic leukemia, having at the same time 10% or more L2 cells, poorer prognosis compared to children, which the number of L2 blasts is less than 10% (3,11,9)

Clinical symptoms in adult patients with acute lymphoblastic leukemia are very diverse, the most common symptoms include weakness, drowsiness, fever not

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associated with infection (in 39% of patients), ossalgia, arthralgia, lymphadenopathy (in 89% of cases), hepatomegaly (83%), splenomegaly (61%). Signs of hemorrhagic syndrome are observed in 67% of ALL cases. In a laboratory study, the following indicators are revealed: hyperleukocytosis above 10 x 10^9/l is noted in 60% of cases, and above 100 x 10^9/l - in 10%; thrombocytopenia less than 50 x 10^9/l - in 60% of patients at the time of diagnosis (3,11,16)

In most cases, patients with hyperleukocytosis above 50 x 10^9/l have significant lymphadenopathy, hepatosplenomegaly, most often - T - cell immunophenotype; in 3-5% of patients, neuroleukemia is diagnosed. The average value of the content of blast cells in the bone marrow (80%) and peripheral blood (50-60%) of patients with AML and ALL is practically the same (4)

Diagnostics. To establish the AL variant, morphological, cytochemical studies, immunophenotyping, cytogenetic and molecular biological studies are performed. (11)

Given the non-specificity of the clinical manifestations of acute leukemia, the diagnosis of the disease is based on the staged application of a complex of laboratory instrumental studies. The first stage - is establishing the very fact that a patient has acute leukemia by means of cytological examination of blood and bone marrow smears. At detection of more than 20% of blast cells in bone marrow smears one can think of acute leukemia. The second stage - is the division of acute leukemia into two groups: acute non-lymphoblastic (myeloid) and acute lymphoblastic leukemia. For this purpose, in addition to cytological, cytochemical and immunological examination of bone marrow samples is carried out. The third stage - is the subdivision of acute leukemia into forms characterized by a specific prognosis and specific features of therapy. For this, along with the above research methods, cytogenetic, molecular genetic, immunohistochemical and some others are used.

It should be emphasized that the morphological assessment of the composition of punctate is basic in the diagnosis of acute leukemia. Without counting the myelogram, it is impossible to interpret the data of cytochemical and immunological studies. The morphological criteria for the characteristics of blasts include: cell size

(ratio of macro-, meso- and microgenerations), shape of nuclei (round, folded, monocytoid), presence of granularity and / or Auer's rods, nuclear-cytoplasmic ratio (high, moderate or low). It is on the basis of morphological features that leukemic myeloblasts and monoblasts are divided into cells with or without signs of maturation (11,17)

Cytochemical studies have a certain value in differences between lymphoblasts and myeloblasts.

Cytochemical markers of granulocyte blasts are peroxidase, lipids detected by Sudan black B, and ASD-chloroacetatesterase. The content of these markers in myeloblasts varies considerably, and sometimes only one of them is detected, most often lipids. In case of a questionable answer, it is imperative to carry out two cytochemical reactions in order to avoid a possible error. The activity of ASD-chloroacetatesterase is significantly lower than that of peroxidase; therefore, the determination of this enzyme is of lower diagnostic value. It is interesting to note that the activity of peroxidase in myeloblasts in children under 15 years old and in patients over 60 years old is lower than in middle-aged people (8)

The most characteristic cytochemical features of lymphoblasts are:

-positive PIC-reaction (to glycogen) in the form of large granules in only 3-5% of cells;

-positive reaction to acid phosphatase;

-variable reactions to β-glucuronidase, naphthyl AS-D-acetate esterase, nonspecific α-naphthyl acetate esterase and α -naphthylbutylesterase;

-negative reactions to myeloperoxidase, naphthyl AS-D-chloroacetatesterase and black pike perch B (for lipids).

With different morphological variants of acute lymphoblastic leukemia cytochemical reactions can be very variable, strict and pathognomonic cytochemical characteristics there are no definite morphological types. (11)

AML diagnostics. The diagnosis of AML is established when 20% or more blast cells are found in the bone marrow punctate. The morphological characteristics of cells in all cases should be accompanied by their cytogenetic study (6,8,12,17)

The diagnosis of acute myeloid undifferentiated leukemia (M0) can be established only on the basis of blast cell immunophenotyping. The diagnosis of acute megakaryoblastic leukemia (M7) can be suggested by cytochemical examination, but must be confirmed by immunophenotyping (CD41-42 or CD62). In other AML variants, immunophenotyping is not absolutely necessary for the diagnosis, but it is required to exclude bilinear leukemia and to determine the initial aberrant immunophenotype, since this will allow monitoring of minimal residual disease in the future. In the absence of the ability to perform immunophenotyping, cytogenetic molecular assays should be diagnosed according to the FAB classification (5,6,10,14)

ALL diagnostics. The diagnosis of ALL is established when 25% or more blast cells are found in the punctate of the bone marrow, morphologically cytochemically characterized as lymphoblasts. The t(9; 22)/BCR-ABL translocation is detected on average in 25% of adult patients. If t(9; 22) / BCR-ABL is detected, tyrosine kinase inhibitors should be included in the chemotherapy program (2,16)

Immunophenotyping of AL makes it possible to determine the linearity of blast cells and the stage of differentiation. Detection of a single-stage expression of antigens on a cell, which normally do not occur together, indicate its aberrant (leukemic) immunophenytype. Antigens detected on lymphoid cells include CD1-5, CD7-10, CD19-20, CD22, CD23, CD56, CD57, CD79a, myeloid- CD11, CD CD13, CD14, CD15, CD33, CD36, CD41, CD42 , CD65, HLA-DR; antigens of early progenitor cells is CD34.

Cytogenetic characteristics of AL. The study of the karyotype of cells in acute leukemias made it possible to identify regular changes characteristic of certain variants of acute leukemia. In almost 90% of patients with AL, cytogenetic abnormalities are found (translocations, deletions, inversions, hyperploidy, the disappearance of one of a pair of chromosomes, and so on), which made it possible to classify AL and isolate their individual forms. Determination of cytogenetic markers of the disease is fundamentally important for both therapy and prognosis of the course of AL.

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The MIC classification (Morphology, Immunology, Cytogenetics), in which cytogenetic data were used along with morphocytochemical and immunophenotypic ones to clarify individual AML variants and determine the prognosis of the disease (11).

Cytogenetic studies reveal various chromosomal abnormalities in acute lymphoblastic leukemia. When analyzing the karyotype, pseudodiploidy (46 chromosomes with structural abnormalities, more often translocations), hyperdiploidy I groups (from 47 to 50 chromosomes), group II hyperdiploidy (more than 50 chromosomes), hypodiploidy for acute lymphoblastic leukemia is not characteristic.

Translocations are very characteristic of acute lymphoblastic leukemia. Specific translocations are t (8; 14) (in patients with B-cell ALL with morphological type L3 with superficial immunoglobulin); t (9;22) or Philadelphia chromosome; t(4; 11); t(l;19) (more often observed with pre-B-ALL). Translocation t(4;11) is most often observed in power cells with lymphoid and myeloid markers. The most important chromosomal abnormality in ALL is translocation t (9;22) with the formation of the chimeric gene BCR-ABL. With this translocation, the ABL gene moves from chromosome 9 to a breakpoint cluster region of chromosome 22. As a result, one of two abnormal protein kinases - p210 or ρ190. Type p210 is more often detected when chronic myeloid leukemia, and type p190 - more often in acute lymphoblastic leukemia.

Cytogenetic studies in acute myeloid leukemia are of great practical importance, since they allow correlate with the clinical features of the disease and more accurately assess the prognosis. Changes in the number of chromosomes (aneuplodia) or their structure (pseudodiploidy), or both, are observed in 50% of cases of acute myeloid leukemia. The most common abnormalities are trisomy 8, monosomy 7, monosomy 21, trisomy 21, loss of X or Y chromosome. At the treatment of acute myeloid leukemia with chemotherapeutic agents, as well as with the use of radiation therapy, a characteristic feature is the partial or complete loss of chromosome 5.

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A number of translocations in AML [t (8; 21), t(15; 17), inv (16)] make up the groups with a favorable prognosis, for which differential treatment programs have been created that allow achieving long-term relapse-free survival. In ALL, the karyotype abnormalities that are unfavorable in prognostic terms include t(9; 22), t(4;11).

As can be seen from the above, the modern algorithm for the diagnosis of acute leukemia variants includes morphocytochemical and immunological approaches, while the diagnostic the value of each method for different options different.

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