Ryazan State Medical University

Department of Faculty Therapy
named after Professor V.Ya. Garmash

HEMATOLOGY

Study guide
for students in the speciality
General Medicine

Ryazan, 2022

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H 53 **Hematology:** study guide for students in the speciality General Medicine/ Compiled by: O.M. Uryasev, A.V. Solovieva, A.S. Pristupa, S.B. Aksentiev; Ryazan State Medical University. – Ryazan: DTS&OP, 2022. – 90 p.

The study guide covers the main diseases of the hematopoietic organs – anemia, acute and chronic leukemia, myeloma. The content of the textbook corresponds to the program questions on hematology of the discipline “Faculty therapy” in the 4th year of the Faculty of General Medicine. The textbook provides up-to-date information about the etiopathogenesis of diseases, clinical manifestations, complications, diagnosis and principles of treatment. The textbook is recommended for students studying in the speciality 31.05.01 General Medicine with an English translation service.

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ГЕМАТОЛОГИЯ

Учебное пособие
для студентов, обучающихся по специальности
Лечебное дело

Рязань, 2022

УДК 616.15 (075.8)
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Г 33

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Г 33 **Гематология:** учебное пособие для студентов, обучающихся по специальности Лечебное дело / Сост.: О.М. Урясьев, А.В. Соловьева, А.С. Приступа, С.Б. Аксентьев; ФГБОУ ВО РязГМУ Минздрава России. – Рязань: ОТСиОП, 2022. – 90 с.

Учебное пособие освещает основные заболевания органов кроветворения – анемии, острые и хронические лейкозы, миеломную болезнь. Содержание пособия соответствует программным вопросам по гематологии дисциплины «Факультетская терапия» на 4 курсе лечебного факультета. В пособии приводятся современные сведения об этиопатогенезе заболеваний, клинических проявлениях, осложнениях, диагностике и принципах лечения. Учебное пособие рекомендуется для студентов, обучающихся по специальности 31.05.01 Лечебное дело с сервисом перевода на английский язык.

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INTRODUCTION

Hematology is a science that studies the blood and hematopoietic system, their structure and functions, diseases and methods of treatment.

Currently, it has become obvious that hematology is one of the most rapidly developing medical specialties - the progress achieved today by practical and experimental hematology allows us, without exaggeration, to call this branch one of the most advanced.

The most important role was played in this by the achievements of the fundamental hematology science. Studies of cytogenetics, molecular and cellular biologists on the model of oncogematological diseases allowed not only to characterize individual nosological forms of blood tumor diseases, but also identified the most important patterns of carcinogenesis in general.

The success of modern practical hematology is largely based on the latest developments in theoretical hematology. Methods of immunophenotyping, classical cytogenetics and molecular genetics have become the standard of examination of a hematological patient. The appearance of fundamentally new types of treatment, drugs that purposefully "correct" genetic and biochemical defects of a tumor cell, led to revolutionary changes in the treatment of previously fatal diseases.

These guidelines are intended for 4th-year students of the Faculty of General Medicine in the specialty 31.05.01 General Medicine, studying the discipline "Faculty therapy".

When studying the issues of diagnosis of blood diseases, the knowledge gained at the Department of Propaedeutics of Internal Diseases is important. The study of the etiopathogenesis of hematopoiesis diseases will require knowledge of anatomy and physiology. A good knowledge of pharmacology will help the student in understanding the issues of modern drug treatment of hematological diseases.

HEMATOPOIESIS

Hematopoiesis (hematopoiesis) is a process consisting of a series of cellular differentiations, as a result of which mature blood cells are formed (Fig. 1).

In an adult organism, there are parent blood cells, or stem cells. It is assumed that they are involved in embryogenesis in a relatively small number. As needed, these cells one by one enter into differentiation, forming a category of more differentiated hematopoietic cells. Stem hematopoietic cells at the stage of maturation are under strict regulatory control, the mechanism of which has not been fully studied. At the early stages of maturation, local factors produced by stromal cells, i.e. the hematopoietic microenvironment, seem to be important. The influence of the microenvironment is carried out by the interaction of stromal and hematopoietic (stem) cells. Such regulatory interactions require direct cellular contacts. In this case, cellular islets are formed, which are groups of hematopoietic cells that lie in a network of processes of reticular cells, adventitial cells of the sinuses of the bone marrow. The mechanism of functioning of such islets is not known. It is possible that locally acting hormones are involved in it, the interaction of cellular surfaces occurs, and transmembrane transitions are formed.

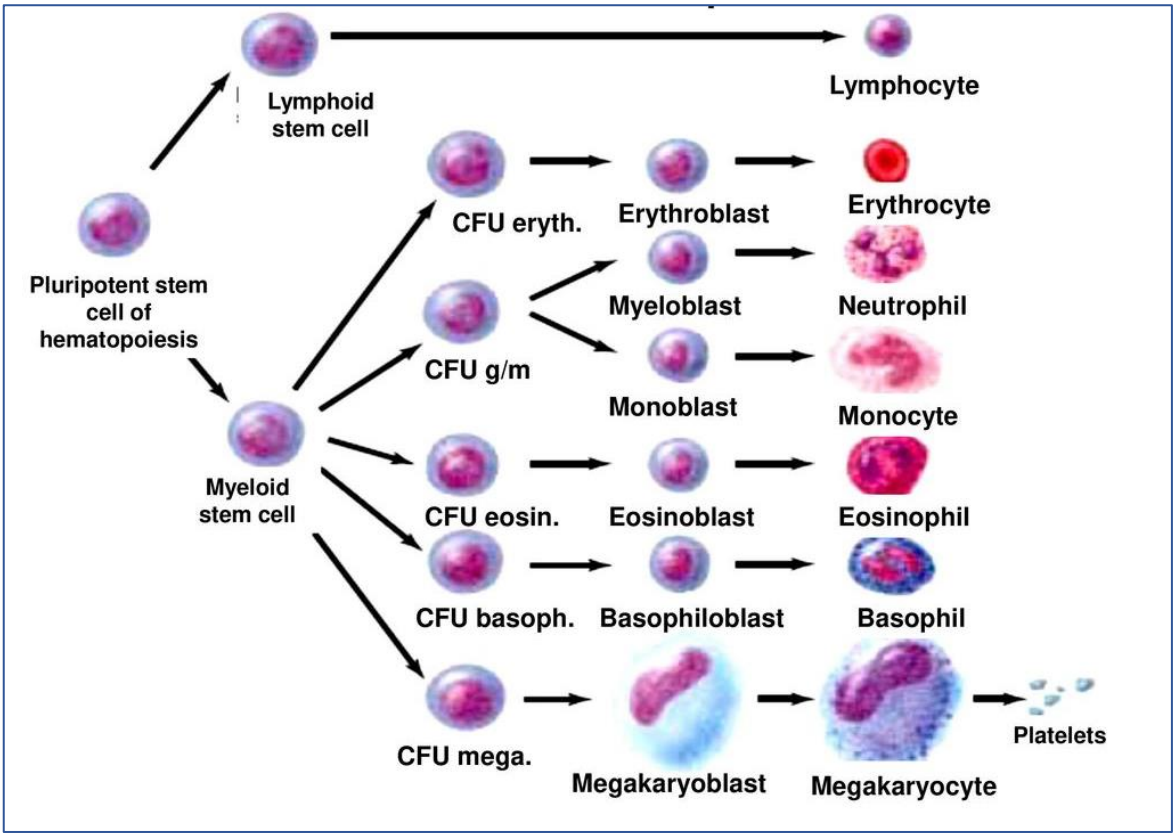


Fig. 1. Scheme of the hematopoiesis process.

Cytokines (interleukins, colony stimulating factor, growth factors), hormones and other humoral factors, such as hemopoietins (erythropoietins, leukopoietins, thrombopoietins) also participate in the regulation of hematopoiesis.

Differentiation of a hematopoietic stem cell into the first morphologically recognizable cells of a particular row is a multi-stage process leading to a significant increase in the number of each of the rows. Meanwhile, there is gradual restriction of the ability of progenitor cells to various differentiations and a gradual decrease in their proliferative potential.

Further on, it was possible to detect poetin-sensitive progenitor cells. The absolute majority of them are in the stage of active proliferation. Morphologically, they, as well as stem cells, are indistinguishable from lymphocytes. The principal feature of poetin-sensitive cells is their ability to respond to humoral regulatory influences. Myelopoiesis and lymphocytopoiesis progenitor cells are located between the stem and poetin-sensitive cells. The existence of these cells has not been strictly proven; however, it has been established that in a number of leukemias, primarily chronic myeloid

leukemia, subleukemic myelosis, erythromyelosis, the only source of tumor proliferation can be the cells that are younger (less differentiated) than poetin-sensitive cells, but more mature than stem cells. Lymphocytic leukemias characterized by simultaneous damage of B and T lymphocytes, i.e. arising from their common precursor, were also identified.

IRON DEFICIENCY ANEMIA

Iron deficiency anemia (IDA) is widespread and accounts for 80-95% of all forms of anemia. They are most often found in children, adolescents and women.

The IDA group includes diseases of various etiologies with the same pathogenetic mechanism characterized by a decrease in the iron content in blood serum, bone marrow and depot. As a result, the formation of hemoglobin (Hb), and subsequently erythrocytes, is disrupted, hypochromic anemia and trophic disorders in the tissues occur. Iron deficiency develops as a result of a discrepancy between the intake of iron into the body and the expenditure (consumption, loss) of iron.

Along with IDA, iron deficiency conditions without anemia are identified - latent iron deficiency - sideropenia - a decrease in the iron content in reserves at normal number of red blood cells and Hb indicators. Latent iron deficiency is often a pre-stage of IDA and, in the absence of iron deficiency compensation, sooner or later leads to anemia. According to WHO data, IDA can be detected in 1.8 billion individuals around the world, and iron deficiency conditions in 3.6 billion. Latent iron deficiency in developed countries is observed in 30% of women, in Japan this indicator reaches 60-70%, in some countries latent iron deficiency occurs in 50-60% of women (Kazakhstan, the Caucasus Republics, Turkmenistan), which, on the one hand, is due to a large number of births in these women and, on the other hand, due to a special diet (low meat content in the diet).

In pregnant women, iron deficiency increases the risk of complications during pregnancy (polyhydramnios, iron deficiency in the fetus) and childbirth (premature birth, premature babies, weakness of the birth forces, frequent ruptures of the birth canal, atonic bleeding). Iron deficiency in a born child is not compensated even

after delivery, because there is an insufficient amount of iron in the milk of such women. Such situation can be conditionally called "accumulation of iron deficiency in generations"; in a child during a period of rapid growth the need for iron increases, the appearance of menstrual blood loss in girls increases the iron deficiency state.

Etiology and pathogenesis of iron deficiency anemia

The etiology of iron deficiency anemia is different. A common pathogenetic factor is a lack of iron in the body (sideropenia), which occurs due to exogenous and endogenous causes:

1. Physiological and pathological blood loss

1. Respiratory diseases.

Pulmonary hemosiderosis. Pulmonary bleeding of various origin (lung cancer, tuberculosis, bronchiectasis, telangiectasia of the bronchial mucosa).

2. Diseases of the cardiovascular system.

Frequent nosebleeds at arterial hypertension.

3. Diseases of the gastrointestinal tract.

Stomach and duodenal ulcers. Stomach and intestinal cancer. Hemorrhoids, rectal fissures, helminthic invasions. Angiomas and telangiectasis. Crohn's disease. Hemorrhagic vasculitis. Diverticulosis, intestinal polyposis. Nonspecific ulcerative colitis.

4. Diseases of liver and portal tract.

Budd-Chiari syndrome with bleeding from dilated veins of the esophagus and stomach. Cirrhosis of liver and extrahepatic portal hypertension (thrombosis, portal vein abnormality) complicated by bleeding from the veins of the esophagus, stomach, hemorrhoids.

5. Kidney diseases.

Kidney cancer. IgA-nephropathy (Berger's disease). Alcoholic nephropathy. Hemorrhagic vasculitis, renal form. Kidney stone disease complicated by hematuria. Goodpasture syndrome. Chronic glomerulonephritis and pyelonephritis with prolonged microhematuria. Bladder polyps and cancer.

6. Diseases of the female genital organs.

Meno- and metrorrhagia in ovarian dysfunction, myoma, cancer of the body of the uterus and cervix, polyposis, abortion, childbirth, endometriosis, thrombocytopenia and thrombohemorrhagic syndrome.

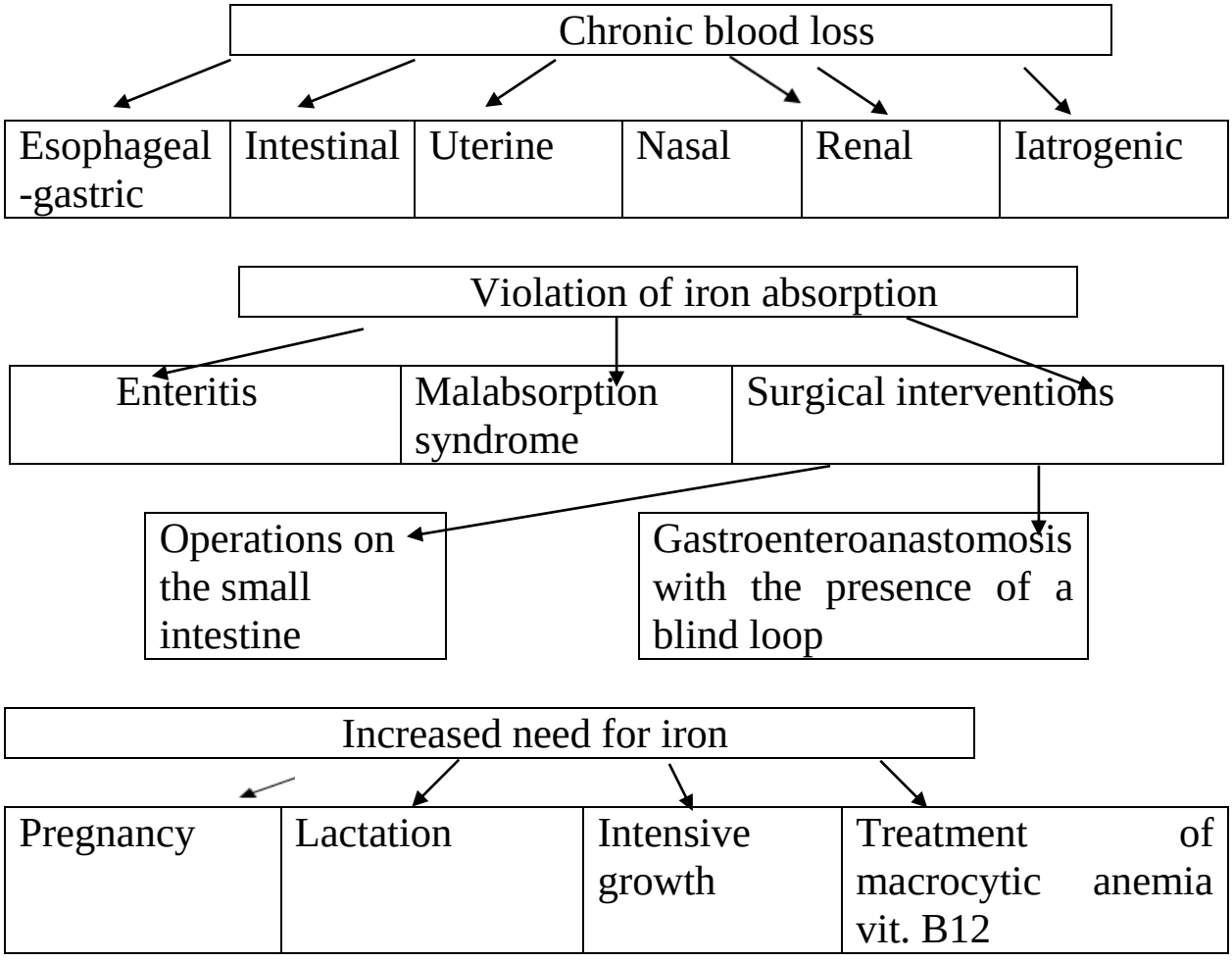
7. *Diseases of the blood system.*

Acute and chronic leukemia complicated by bleeding. Aplastic anemia complicated by bleeding. Paroxysmal nocturnal hemoglobinuria.

8. *Hemorrhagic diathesis (hereditary, acquired).* Blood clotting disorders, thrombocytopenia, thrombocytopathy, iatrogenic bleeding.

2. Lack of iron in food - vegetarian diet.
3. Increased iron consumption. Puberty, pregnancy, lactation, intensive sports.
4. Congenital iron deficiency. In premature infants, mothers who suffer from iron deficiency.
5. Iron absorption disorders. Anenteral condition, chronic enteritis, malabsorption disease.

Figure 2 clearly shows the etiology of IDA.



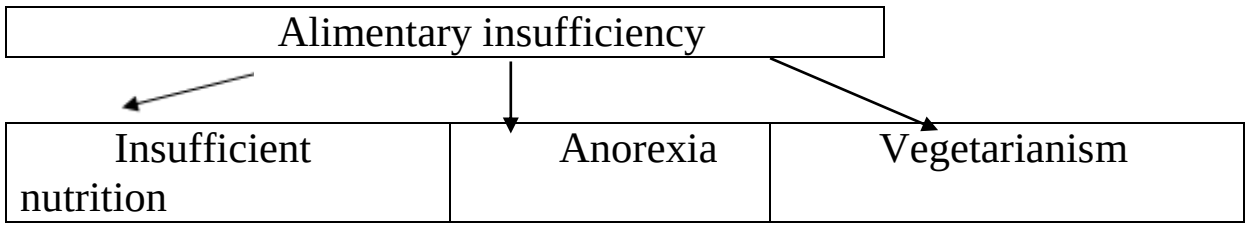


Fig. 2. Etiology of IDA.

Physiology of iron metabolism in the body

The total iron content in the body of a healthy person averages 4-5g, while the main part (about 2.7 g) refers to hemoglobin iron. Iron is found in the lungs, spleen, liver and muscles in the form of myoglobin.

Iron is found in many food products with which it enters the body. Soy, peas, spinach, prunes, raisins, rice, bread, meat, fish, liver and other products contain a large amount of iron. The largest amounts of iron are absorbed in the gastrointestinal tract from veal, fish, less from vegetable products (1-7%). Iron is absorbed better from proteins containing heme (veal), worse from proteins containing ferritin and hemosiderin (liver). The use of animal and vegetable products significantly increases the iron absorption. Iron absorption slows down with low protein content in the diet, high fat content in the diet and the use of a large amount of tannin (strong tea, coffee).

Iron absorption in the body increases with blood loss, pregnancy, increased muscle work, hypoxia.

In gastritis with reduced secretory function the absorption of iron almost does not change. Studies with labeled iron have shown that the level of hydrochloric acid practically does not affect the absorption of dietary iron, both with sufficient iron saturation of the body and with its deficiency.

Iron absorption in the gastrointestinal tract begins with the duodenum and continues in the small intestine (Fig. 3). The process of iron absorption includes three stages:

1. - penetration of iron into the mucous membrane from the bowel lumen;
2. - penetration of iron from the intestinal mucosa into plasma;
3. - filling of iron reserves in the mucous membrane and the effect of these reserves on absorption.

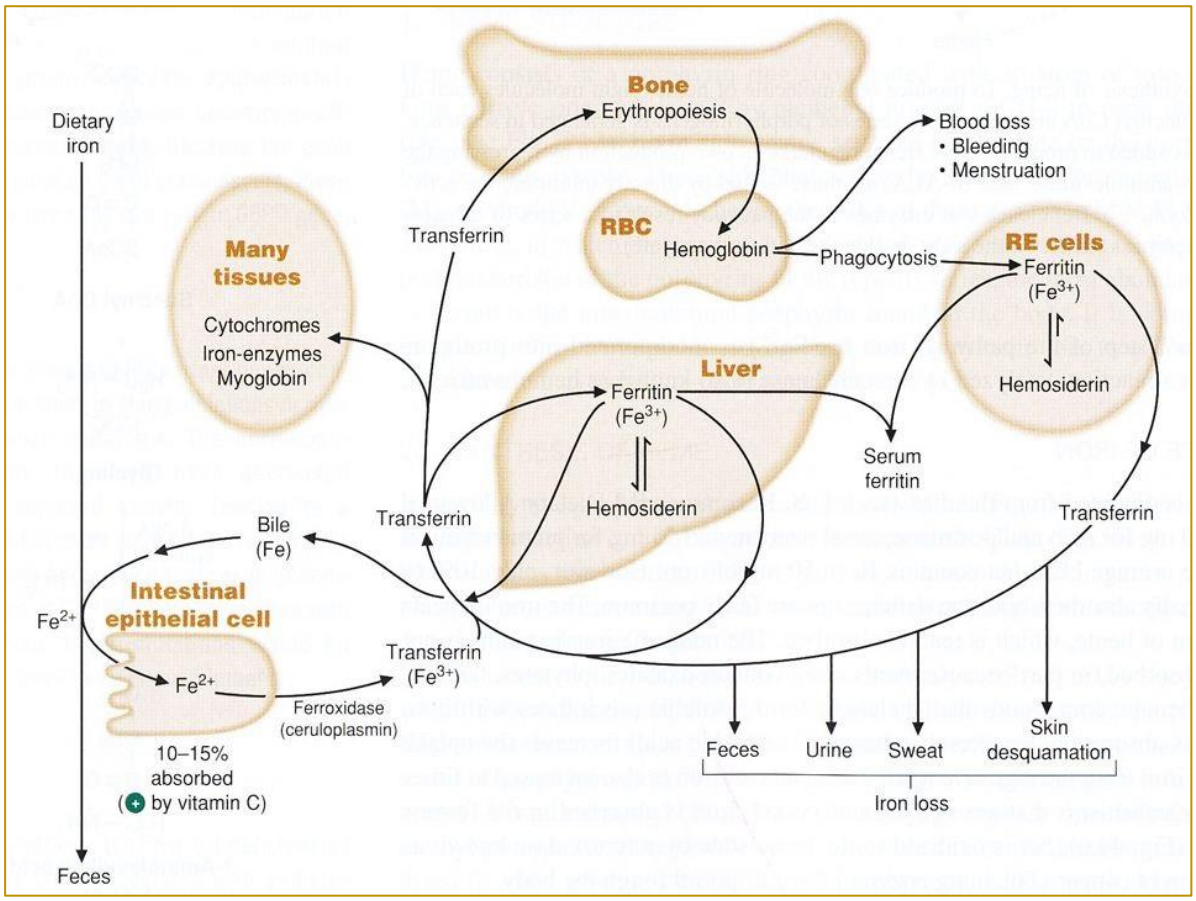


Fig. 3. Iron metabolism in the body.

With a normal iron content in the body, a significant part of it passes through the intestinal mucosa into the blood stream, while a certain part is retained in the mucosa. With an increased need for iron in the body, the rate of its entry into the plasma from the mucosa approaches the rate of penetration into the intestinal mucosa. At the same time, iron is practically not deposited in the intestinal mucosa, most of it ends up in plasma.

With an excess of iron in the body, the main part of the iron that has penetrated into the mucosa remains in the intestinal mucosa. The intestinal epithelial cell, filled with iron, moves from the base to the end of the villi, then it is exfoliated and discharged together with the non-absorbed iron.

Bivalent iron salts are better absorbed in the intestine, especially at high concentrations of it in the intestine. Trivalent iron is almost not absorbed in the body.

The age of people does not affect the intensity of iron absorption in the intestine. It is oxalates, phosphates and tannin that slow down the absorption of iron. Ascorbic acid and fructose contained in

vegetables and fruits enhance the absorption of iron. In addition, the absorption of iron is increased by succinic, pyruvic acid.

After absorption, iron binds to transferrin, which transfers iron to the erythrocaryocytes of the bone marrow.

To preserve the excess of iron in the body, the ferritin protein is used, containing up to 3000 iron atoms in 1 molecule. The greatest amount of ferritin is found in the liver, muscles, less in plasma and almost in all cells of the body.

The second protein containing an iron reserve is hemosiderin. It is contained in macrophages of the spleen, liver cells. However, only a small part of the iron of parenchymal cells is used for erythropoiesis.

The loss of iron from the body in men and non-menstruating women is approximately 1 mg. In healthy menstruating women, iron loss during one menstruation ranges from 15 to 250 mg. Women lose at least 800-1000 mg of iron during pregnancy, childbirth and lactation. One pregnancy and lactation in a healthy woman does not lead to a significant decrease in iron reserves in the body.

There are 3 stages in the formation of iron deficiency:

1. Prelatent deficiency of tissue iron reserves, determined by the absence of hemosiderin in bone marrow macrophages; an indirect sign is an increase in intestinal iron resorption.
2. Latent iron deficiency, manifested by hyposiderinemia, an increase in the total and latent iron-binding capacity of blood serum and the concentration of protoporphyrin in erythrocytes.
3. The manifest form of iron deficiency is iron deficiency anemia, which differs from the previous stages by a significant decrease in the iron content in the body, a violation of hemoglobin synthesis and clinical manifestations of the disease.

Prelatent iron deficiency is characterized by the following signs: anemia is absent, the hemoglobin level is normal; sideropenic syndrome is absent, since the tissue iron fund is preserved; serum iron level is normal; iron reserves (depots) are reduced.

A decrease in iron reserves can be detected using the following laboratory methods:

a) determination of serum ferritin by radioimmune method. The ferritin content in the blood is 85-130 mcg/l in men, 58-150 mcg/l in women. The ferritin level of less than 12 mcg/l reliably indicates a decrease in iron reserves.

b) desferal test - 500 mg of desferal is injected intramuscularly to the patient, after which the iron content in the daily amount of urine is determined. Desferal is a complexon, which is a product of the vital activity of actinomycetes, capable of combining with depot iron (ferritin and hemosiderin), then this iron is excreted with urine. In a healthy person with normal iron content in the depot, the iron content in the daily urine after administration of desferal is 0.6-1.6 mg. With a decrease in iron reserves, the indicator is lower (0.4 mg or less);

c) sternal puncture - with a decrease in the iron depot, the number of sideroblasts in the bone marrow significantly decreases. Sideroblasts are erythrocaryocytes containing iron granules; they are detected with a special staining of the sternal punctate by Perls' method. Normally, the content of sideroblasts in the bone marrow is 20-50%, with a decrease in iron reserves their number is 15% or less.

Latent iron deficiency is diagnosed based on the following signs:

- anemia is absent, the hemoglobin content is normal;
- there are clinical signs of sideropenic syndrome due to a decrease in the tissue fund of iron;
- the content of serum iron is reduced, which reflects a decrease in the transport fund of iron.
- the total iron-binding capacity of blood serum **(TIBC)** is increased.

If these changes progress, and iron deficiency is not replenished, anemia develops.

Clinical picture

The mechanism of development of clinical manifestations of IDA remains underinvestigated. First of all, of great importance are tissue hypoxia, a decrease in the activity of many enzymes (respiratory, hematopoietic enzymes, myocardium), development of dystrophic changes.

It is necessary to find out how the disease began (acutely or gradually), whether relatives had anemia, what medications the patient had been taking (anemia is caused by many medications and alcohol). IDA is characterized by a decrease in appetite, pallor of skin, muscle hypotension, weakness, increased fatigue. With deep anemia, epithelial tissue (rough skin, spoon-like brittle nails, coilonychia, hair

loss) and mucous membranes (atrophy of lingual papillae, erosion in the corners of the mouth) are affected, a perverted taste (picachlorotika) appears. Coilonychia is a sign of a pronounced and long-term iron deficiency, therefore it does not always occur with IDA (Fig.4). The tendency to infectious-inflammatory diseases is increased.

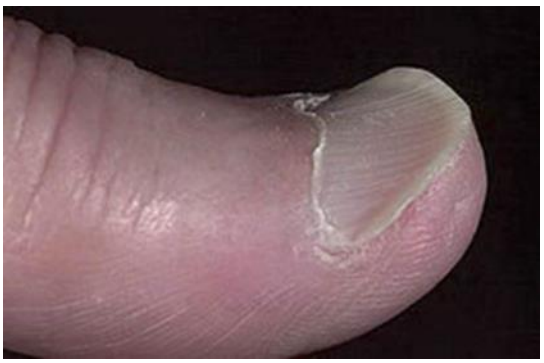


Fig. 4. Coilonychia

With an objective examination, the pallor of skin and visible mucous membranes is usually noted, there may be cracks in the corners of the mouth (chilosis). In the differential diagnosis of anemia, it is important to remember to identify symptoms such as "vascular spider", "liver palms", the symptom of "butterfly" (systemic lupus erythematosus), nail changes. It is necessary to take into account the state of turgor and elasticity of skin, the presence of scratches, various rashes (hemorrhages, telangiectasia), changes in joint configurations and the volume of movement in them.

The tongue (polished tongue in IDA), oral mucosa (hemorrhages, gum condition), presence of telangiectasia in Rendu-Osler disease, sclera (presence of ictericity, Lukin-Liebman symptom) and other organs and systems are carefully examined. Then it is necessary to conduct a survey of the condition of all groups of lymph nodes available for palpation, which is of great diagnostic importance. The mandibular, cervical, supraclavicular and inguinal groups of lymph nodes are consistently palpated, their size, consistency and mobility are determined. The doctor should carefully examine the mammary glands, thyroid gland, its size, consistency.

Changes in the cardiovascular system in IDA are observed in many patients. During auscultation of the heart, diminished 1st tone and apical systolic murmur are noted.

Diagnostics of IDA

Laboratory data are the most characteristic feature of IDA. The Hb content in IDA can range from 110 g/l to 20-30 g/l depending on iron deficiency. The content of red blood cells can be normal or reduced to 1,5-2,0*10^{12}/L.

Hemoglobin and hematocrit are the main indicators of anemia severity. It should be remembered that with acute bleeding both erythrocytes and plasma are depleted, so the concentration of hemoglobin and hematocrit may initially remain normal and decrease only after a while - after the plasma volume has recovered at least partially.

The content of reticulocytes is an indicator of erythropoiesis activity. The content of reticulocytes is usually expressed as a percentage of the number of red blood cells; some automatic analyzers give the absolute content of reticulocytes in a microliter. The upper limit of the norm of reticulocyte content is 2%, that is, approximately 100,000 μl-1. Reticulocytosis in IDA indicates that the ability of the bone marrow to produce erythrocytes is preserved and, therefore, the cause of anemia is blood loss or hemolysis or the patient received iron preparations before the study. The absence of reticulocytosis in anemia indicates the insufficiency of red blood cell production.

Microscopy of a blood smear is mandatory for any anemia. There are differences in the size of erythrocytes (anisocytosis) and anomalies of their shape (poikilocytosis), microcytosis. Leukocytes and platelets must be examined.

The content of leukocytes in hypochromic anemia tends to decrease, most often due to a moderate decrease in the content of neutrophils. The platelet count in most cases of IDA is within the normal range, less often increased, especially with blood loss.

There are no significant pathological signs in the bone marrow, while the cellular composition of the bone marrow, as a rule, is within the normal range. In some cases, cytological examination of the bone marrow reveals a moderate predominance of red germ – an increase in the number of basophilic and polychromatophilic erythrocaryocytes due to a decrease in the number of oxyphilic forms, the number of sideroblasts - erythrocaryocytes containing iron granules is reduced.

Serum iron (normally 10.74-21 mmol / L) decreases to 1.8-5.4 in severe IDA, to 10.5-7.2 in mild form.

The iron-binding capacity of blood serum (normally - 44.8-71.6 mmol/L) increases with IDA.

The percentage of transferrin saturation in hypochromic anemia decreases (normally 12-300 mcg/l).

Desferal test: 500 mg of desferal is administered in / m, after which the iron content in the daily urine is determined. Normally, excretion of iron is 0.8 -1.3 mg, in IDA it is decreased to 0.2 mg/day and below.

It is mandatory that women are examined by a gynecologist to exclude such possible causes of IDA as uterine fibromatosis, tumors of the cervix, ovaries, endometriosis and others.

It should be remembered that in the diagnostic search with IDA, an endoscopic examination of the duodenum, stomach and esophagus is necessary to exclude such possible causes of bleeding as cancer of the Vater's ampulla, peptic ulcer, Menetrier's disease, Weber-Rendu-Osler, hernias of the esophageal hiatus, diverticula and tumors of the esophagus, varicose veins of the esophagus.

In patients with an operated stomach, hypochromic anemia may develop after 6-12 months after extensive resections (subtotal, total) of the stomach due to impaired iron absorption.

Rectoromanoscopy has not lost its significance when examining patients with blood secretions from the rectum. Hypochromic anemia is observed in 50% of patients with colon cancer.

In the diagnosis of anemia of unclear etiology, it is necessary to use such a simple method of intestinal examination as a coprological study. The reaction of Weber and Gregersen reveals latent fecal blood only at a daily blood loss of more than 15-20 ml.

It should also be remembered about the rarer causes of hypochromic anemia. So, one of the "hematological masks" of hypernephroma may be hypochromic anemia.

Hypochromic anemia is observed in thyroid, bladder, prostate cancer, and occasionally - in lung cancer - it is necessary to include a urological ultrasound examination of the kidneys and urinary bladder in the examination plan of patients with hypochromic anemia of unclear genesis.

If hypochromic anemia with high iron content of blood serum is detected in a patient, it is necessary to exclude chronic lead intoxication. In such patients, it is necessary to perform a detailed

study of the professional history (the presence of contact with occupational hazards).

Demidova A.V. points out the causes of errors when establishing the diagnosis of the IDA:

1) Determination of the iron content in blood serum and other indicators of the iron transport fund was carried out against the background of taking iron preparations. At least a 7-day interval is required between discontinuation of intake of the iron preparation and this study, otherwise the indicators will be artificially elevated.

2) Qualification errors of a laboratory assistant doctor, and if there are reasons for IDA, an internist doctor.

3) The lack of methods of research of transport and reserve funds of iron in this medical institution.

4) The indication of a sternal puncture, in which the staining of bone marrow smears for iron is not provided. Without staining the smears, the puncture is not very informative in IDA.

5) Random treatment of anemia with various antianemic drugs before an accurate diagnosis is established.

Differential diagnosis of iron deficiency anemia

In the diagnosis, first of all, it is necessary to exclude hypochromic conditions proceeding with a high content of iron (thalassemia, anemia associated with impaired synthesis of porphyrins and heme).

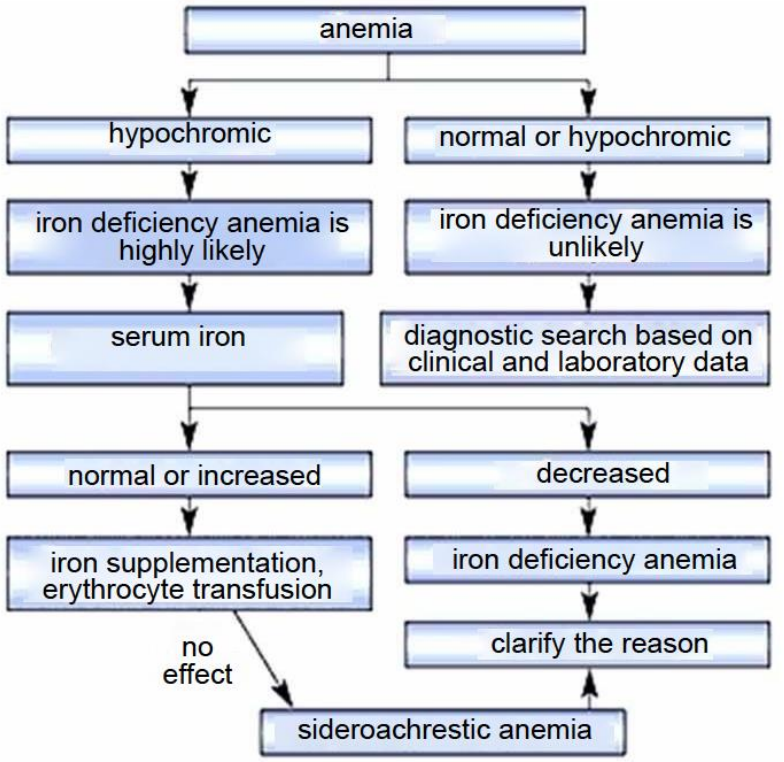


Fig. 5. Algorithm for diagnosing iron deficiency anemia

When the diagnosis of iron deficiency anemia is established, it is necessary to clarify its genesis. Sometimes the cause of the deficiency cannot be identified and then it is said to be an essential form of IDA. However, it is necessary to remember that the "essential" form of IDA is extremely rare and it can be diagnosed only after a very thorough examination of the patient, after excluding all pathological conditions occurring with iron deficiency.

When studying the anamnesis of patients, it should be kept in mind that iron deficiency often occurs as a result of long-term blood loss, but it can also be associated with insufficient incomee of it into the body. It should be emphasized that iron deficiency in the body can be caused by several reasons at the same time.

Taking into account the high frequency of iron deficiency anemia in women, it is necessary to clarify the gynecological history when collecting anamnesis: the age of patients, the onset of menstruation, the duration of the menstrual cycle, the amount of blood loss during them, as well as to take into account the number of pregnancies and childbirth, the length of intervals between them, the number of abortions and the approximate amount of blood loss during those.

The cause of iron deficiency anemia in both men and women may be frequent donation. When donating 400 ml of blood, the donor loses 200 mg of iron.

It is necessary to take into account the possibility of alimentary genesis of anemia, which can develop in the people who have kept to a diet containing small amounts of dietary iron (vegetarianism) for a long period of time.

Various helminthic invasions can be the cause of hypochromic anemia: hookworm infection (Transcaucasia, Central Asia), strongyloidosis (Transcaucasia, Ukraine, sometimes Russia). Chronic blood loss in these patients occurs as a result of traumatization of the intestinal mucosa by parasites attached to it or the development of erosive and ulcerative gastroduodenitis (strongyloidosis).

The diseases and operations undergone by patients during their life, especially gastric and intestinal resections, the presence of chronic diseases of stomach, intestines, liver and pancreas are of great importance.

It should be remembered that patients often, out of a sense of false modesty, do not tell the doctor about changes in the intestinal habits (stool frequency, its character, color, the presence of an admixture of blood in the feces), so the doctor is obliged to question the patient carefully and actively. Many patients hide their addiction to alcohol, so the doctor should clarify this point when questioning the patient.

In the process of questioning the doctor can often identify a possible source of bleeding: upper respiratory tract, bleeding from the mouth, nose, hemoptysis when coughing, an admixture of fresh blood in the feces, long-lasting profuse menstruation, uterine bleeding, etc., which in many cases will facilitate the diagnostic search. But often the patient cannot name a possible cause of anemia.

Treatment of iron deficiency anemia

Before proceeding with the treatment of IDA, it is necessary first of all to identify and establish the cause of blood loss. Treatment of such patients is carried out by hematologists, if necessary, together with doctors of other specialties (surgeon, gynecologist, proctologist, etc.).

The nutrition of patients should be diverse and complete. The daily diet of patients should include a sufficient amount of animal

proteins (at least 200g of meat per day), as well as vegetables and fruits containing large amounts of vitamins (citrus fruits, pomegranates, currant, cabbage, carrots).

In the treatment of anemia, the following stages are distinguished:

1. anemia arresting,
2. replenishment of iron reserves in the body (saturation therapy),
3. anti-relapse treatment.

Principles of treatment:

- Correct the causes (diseases) underlying iron deficiency.
- Compensate for iron deficiency in blood and tissues.
- It is useful to keep to a diet, but this is not enough: you should know that it is impossible to cure IDA with a diet. The greatest amount of iron is contained in the food of animal origin: meat, fish, eggs.
- One should not resort to blood transfusions without vital indications (they are respiratory, cardiovascular insufficiency, anemic coma and precoma). Any unjustified transfusion of blood preparations, even a single one, carries a threat of transfusion infections (viral hepatitis, HIV infection, etc.), the appearance of allergic reactions as a result of sensitization of patients.
- Only iron preparations should be used. The additional prescription of group B vitamins, including B_{12}, is not justified.
- Parenteral administration of iron preparations should be limited to absolute indications:

- violation of iron absorption in intestinal pathology (enteritis, resection of the small intestine, malabsorption syndrome, gastric resection by Billroth II with the exclusion of the duodenum),
- exacerbation of peptic ulcer,
- intolerance of iron preparations for oral administration, which does not allow further continuation of treatment.

Rapid saturation of the body with parenteral administration of iron, for example, in patients with IDA who are about to undergo surgical interventions, can hardly be considered appropriate, since this mostly refers to planned operations when treatment of IDA can be safely carried out with tablet preparations.

With parenteral administration of iron preparations (ferrumlek), complications are sometimes observed: allergic dermatitis, arthralgia, fever, muscle pains, phlebitis, urticarial fever, Quincke's edema, rarely anaphylactic shock. The risk of complications can be reduced if the drug is administered slowly (for at least 10 minutes).

- Iron preparations are prescribed for a long time. The concept of a "course of treatment" does not exist. Treatment is carried out until anemia and tissue iron deficiency disappear. With the normalization of red blood, patients should take iron preparations for another month in full or half the therapeutic dose, depending on the tolerability of the drugs and the blood picture.
- In case of persistent blood loss (meno- and metrorhagias), anti-relapse treatment of iron preparations in full or half dose should be carried out, starting it 2 days before menstruation and stopping to take the drug 2 days after its termination.
- When selecting an iron preparation and an optimal dosage regimen, it should be kept in mind that an adequate increase in the hemoglobin index in the presence of IDA can be ensured by daily income of 30 to 100 mg of divalent iron into the body. Considering that iron absorption increases to 25-30% during IDA (with normal reserves of iron in the body 3-7%), it is necessary to prescribe from 100 to 300mg of divalent iron per day. The use of higher doses is unreasonable, since the absorption of iron does not increase. Thus, the minimum effective dose is 100 mg, the maximum is 300mg of divalent iron per day. Individual fluctuations in the required amount of iron are due to the degree of iron deficiency in the body, depletion of reserves, the rate of erythropoiesis, absorbing capacity, tolerability and other factors. Therefore, when choosing a drug, one should focus not only on the total amount, but also on the amount of divalent iron, which is the only kind absorbed in the intestine.
- Prolonged preparations in which iron is in a divalent form are preferred. The introduction of a number of prolonged preparations of ascorbic acid into the composition is advisable, since it improves the absorption of iron. These requirements are fully met by sorbifer durules, 1 capsule of which contains 100 mg of elemental iron and 60 mg of ascorbic acid. 1 capsule is administered 30 min before meals 1-2 times a day, and with a slight iron deficiency - once a day.

- The main iron preparations used are sorbifer, ferrumlek (in this case in tablet form). Maltofer (polymaltose complex of iron), actiferrin, ferretab have a good effect. It is advisable to take iron preparations in between meals. Before and after taking iron, it is not recommended to give tea, fatty and flour products in order to avoid the formation of insoluble compounds that impair the absorption of iron. With proper treatment, the average hemoglobin growth rate is 1 g/day. The treatment efficacy is evidenced by an increase in reticulocytes after 5-10 days and normalization of Hb after 1-2 months.

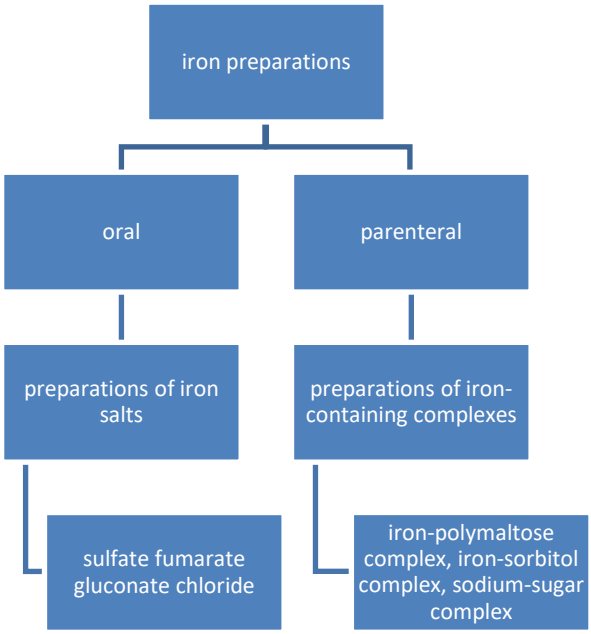


Fig. 6. Iron preparations.

Normal response to iron therapy:

* subjective improvement 48 hours after the start of treatment;
* maximum increase in reticulocytes after 9-12 days;
* normalization of hemoglobin content after 6-8 weeks.

Causes of failures in the iron preparations treatment:

* absence of iron deficiency (incorrect diagnosis of the nature of hypochromic anemia and erroneous administration of iron preparations);
* insufficient duration of treatment with iron preparations;
* insufficient dosage of iron preparations;
* impaired absorption of iron preparations administered orally (Fig. 7);

* simultaneous administration of drugs that disrupt the absorption of iron;

* ongoing chronic blood loss from unidentified sources (most often from gastrointestinal tract);

* combination of IDA with other anemic syndromes (vitamin B_{12}-deficient, folic-deficient anemia).

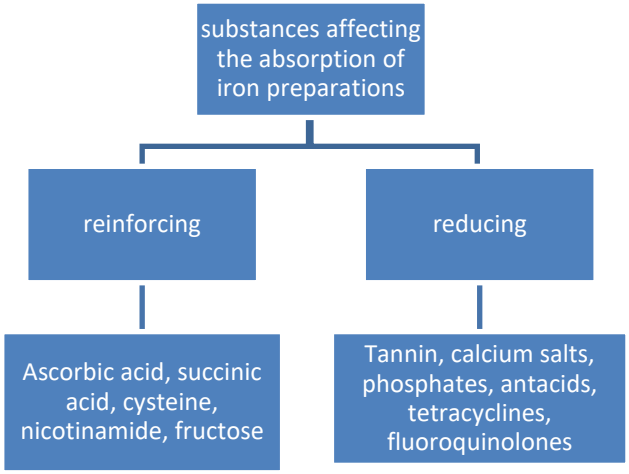


Fig. 7. Substances affecting the absorption of iron preparations.

Sometimes patients conceal from the doctor the fact of untimely termination of treatment due to experiencing some kind of discomfort from taking iron preparations. Many patients are adapted to anemia and do not want to be treated. In order to avoid such situations, constant contact of the doctor with the patient is necessary (including explanatory work on the consequences of chronic iron deficiency). The unsatisfactory effect of ferrotherapy is an argument in favor of surgical elimination of the blood loss source (in uterine fibromatosis, hemorrhoids, etc.).

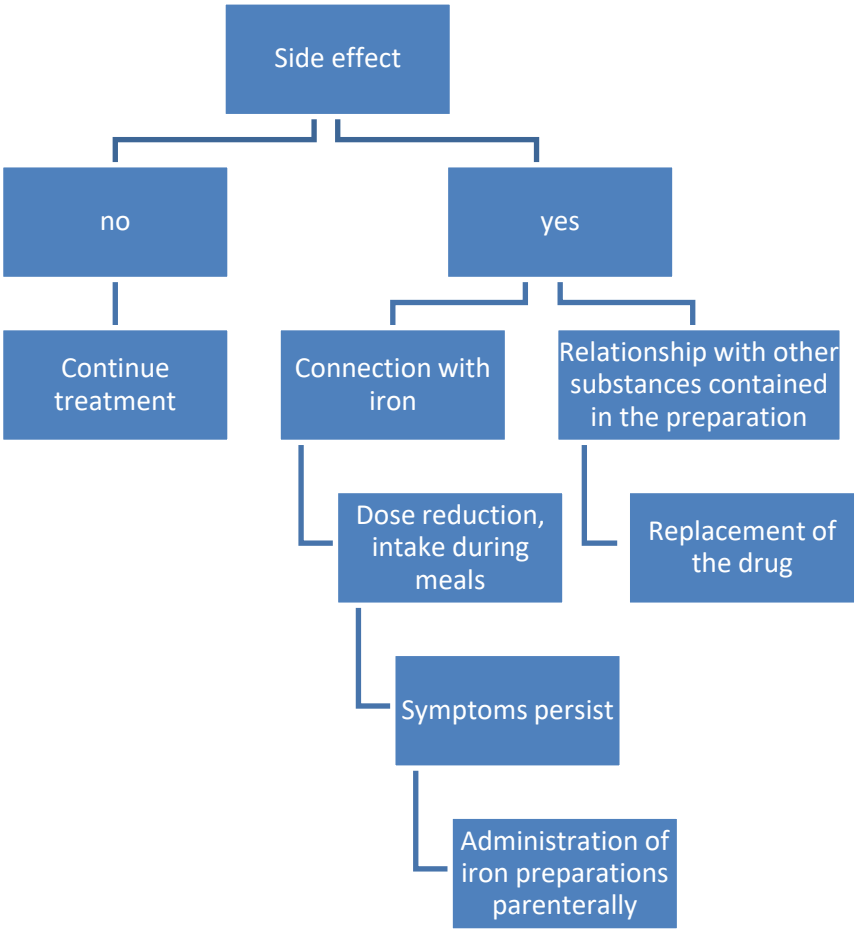


Fig. 8. Tolerability of oral iron preparations.

Prevention of iron deficiency anemia

Primary prevention of IDA is carried out when iron deficiency (latent form of IDA) is detected in high-risk groups: women of childbearing age suffering from profuse and prolonged menstruation with a short menstrual cycle, permanent donors, pregnant women, women with repeated pregnancies following one after another with short intervals (1-2 years), especially when a woman before pregnancy suffered from profuse menstrual blood loss.

Pregnant women are recommended to take iron preparations in two-week courses monthly if they have iron deficiency, especially in the II -III trimesters of pregnancy. Preventive treatment is also carried out for new mothers during lactation. Iron preparations are prescribed at a dose equal to half of the therapeutic dose.

Permanent donors need to monitor the indicators of iron metabolism at least 2 times a year. After blood donation, preventive oral administration of iron preparations for 3-4 weeks in a half therapeutic dose is recommended to donors.

Secondary prevention or anti-relapse treatment of patients with IDA is carried out after the course of treatment. It consists in prescribing iron preparations in short courses of 7-10 days monthly to patients with IDA and recurrent hemorrhages (menorrhagia, recurrent hemorrhoidal bleeding, in the presence of a hiatal hernia, etc.).

All patients with IDA should be under the dispensary supervision of a hematologist with mandatory blood analysis, examination of the iron content of blood serum at least 2 times a year. If necessary, patients are consulted by a therapist, gynecologist, surgeon and other specialists.

B_{12} -DEFICIENCY ANEMIA

B_{12}-deficiency anemia belongs to the group of megaloblastic anemia. This is a clinical and hematological symptom complex that unites a group of diseases characterized by macrocytic anemia and megaloblastic type of hematopoiesis.

From a biochemical point of view, the primary condition in this case is a violation of DNA synthesis: cells stop developing in the S-phase of the cell cycle and cannot complete the division process. As a result, there is an accumulation of large cells "waiting" for mitosis and their premature death. Most often, megaloblastosis is caused by insufficient vitamin B_{12} (cobalamin) and folic acid, as well as taking medications that inhibit DNA synthesis.

Vitamin B_{12} (cobalamin) is produced by microorganisms-inhabitants of root crops and legumes, and is present in the muscles and parenchymal tissues of animals that feed on these plants. A person receives cobalamin with animal food. The total content of cobalamin in the human body is 2-5 mg, and since its daily loss is very small (2-5 micrograms/day), in case of complete cessation of ingestion, its reserves (mainly in the liver) are sufficient for 2-3 years. For the absorption of vitamin B_{12}, an internal factor (IF) is required, which is secreted by the parietal cells of the stomach. The cobalamin+IF complex moves to the distal parts of the ileum where cobalamin is absorbed. In the blood, cobalamin binds to transcobalamin II, a transport protein that delivers cobalamin to target tissues. 1% of cobalamin is absorbed without the formation of a complex with an internal factor. Folates (group B vitamins) are found in leafy

vegetables (legumes, lettuce, spinach), fruits, mushrooms, animal proteins. Folate reserves in the human body are 5-10 mg, and their daily loss is 100-200 mcg, therefore, complete cessation of folate intake leads to their deficiency after 1-2 months. Folates are also absorbed in the distal sections of the small intestine.

Etiology and pathogenesis of B_{12}-deficiency anemia

Megaloblastic erythropoiesis is conditioned by a deficiency of vitamin B_{12} and folic acid, which can develop on the basis of various mechanisms: frequent infections, incomplete nutrition, feeding with goat's milk (in babies), celiac disease (intestinal malabsorption), chronic diseases of the gastrointestinal tract and liver, helminthic infestation (broad tapeworm, etc.).

Megaloblastic anemia is characterized by a weakening of DNA synthesis, as a result of which the division of all rapidly proliferating cells (hematopoietic cells, skin cells, gastrointestinal cells, mucous membranes) is disrupted. Hematopoietic cells are among the most rapidly multiplying elements, so anemia, as well as neutropenia and thrombocytopenia often come to the foreground in the clinical picture.

In addition, cyancobalamin is a coenzyme in the reaction of conversion of methylmalonyl-CoA to succinyl-CoA. This reaction is necessary for the metabolism of myelin in the nervous system, in connection with which, with cyancobalamin deficiency along with megaloblastic anemia, damage to the nervous system is noted, while with folate deficiency only the development of megaloblastic anemia is observed.

Complete depletion of reserves in the absence of intake (impaired absorption, with a vegetarian diet) occurs only after 1000 days. Folate reserves are 5-10 mg, the minimum requirement is 50 mcg per day. Megaloblastic anemia can develop after 4 months of complete absence of folate intake with food.

Clinical picture of B_{12}-deficiency anemia

The clinical picture is characterized by symptoms of the main disease. Since anemia with vitamin B_{12} and folic acid deficiency develops gradually over a long period of time, patients are usually well adapted to low hemoglobin levels. Clinical symptoms of anemia are not specific: weakness, fatigue, shortness of breath, dizziness, palpitations. Patients are pale, subicteric. There are signs of glossitis -

with areas of inflammation and papillary atrophy, raspberry tongue, there may be an increase in the spleen (the result of extramedullary hematopoiesis) and liver. A typical picture of Hunter's glossitis is characterized by the appearance of bright red areas of inflammation at the tip and along the edge of the tongue, sometimes covering its entire surface ("scalded" tongue). Aphthous rashes and fissures are often observed on the tongue. Similar changes can spread to the gums, cheek mucosa, soft palate, pharynx and esophagus. The intake of food and medicines is accompanied by a burning sensation and pain. Sometimes patients complain of a feeling of weight in the epigastric region, loss of appetite and bowel disorders. Gastric secretion is sharply reduced. In FGS atrophy of the gastric mucosa is detected, which is confirmed histologically.

Neurological symptoms of vitamin B_{12} deficiency vary depending on the severity of the pathology. Early signs include disfunction of the posterior horns of the spinal cord with loss of proprioception and vibration sensation. Patients move with difficulty, spreading their legs wide when walking. Later, they develop lesions of the pyramidal, spinal-cerebellar and spinal-thalamic tracts, accompanied by muscle weakness, progressive spasticity, hyperreflexia, and scissor gait. Peripheral nerves can also be damaged due to the loss of deep tendon reflexes, cranial palsy, loss of control over the sphincters. With prolonged vitamin B_{12} deficiency, dementia and neuropsychic disease occur. Neurological symptoms with vitamin B_{12} deficiency can occur without anemia.

Thus, B_{12}-deficient anemia is characterized by the triad:

• blood damage,

• GIT lesion,

• nervous system impairment.

Diagnosis of B_{12}-deficiency anemia

1. Clinical blood test:

- decrease in the number of red blood cells
- decrease in hemoglobin
- increase in color index (above 1.05)
- macrocytosis
- basophilic stippling of erythrocytes, the presence of Jolly bodies and Cabot’s ring bodies in them
- the appearance of orthochromic megaloblasts

- reduction of reticulocytes
- leukopenia
- thrombocytopenia
- reduction of monocytes
- aneosinophilia.

2. There is a typical picture in the stained smears: along with the characteristic oval macrocytes, there are erythrocytes of normal size, microcytes and schizocytes - poikilocytosis and anisocytosis.

3. The level of bilirubin in the serum is increased due to the indirect fraction.

4. Bone marrow puncture is mandatory, since such a picture on the periphery can be with leukemia, hemolytic anemia, aplastic and hypoplastic conditions (however, it should be noted that hyperchromia is characteristic of B_{12}-deficient anemia). The bone marrow is cellular, the number of nucleated erythroid elements is increased 2-3 times against the norm, however, erythropoiesis is ineffective, which is evidenced by a decrease in the number of reticulocytes and erythrocytes on the periphery and shortening of their life expectancy (normally an erythrocyte lives 120-140 days). Typical megaloblasts are found - the main criterion for the diagnosis of B_{12}-deficiency anemia. These are cells with "nuclear-cytoplasmic dissociation" (with a mature hemoglobinized cytoplasm, there is a soft, reticulated nucleus with nucleoli); large granulocyte cells and giant megakaryocytes are also found.

The diagnosis is established on the basis of the clinical picture, the picture of peripheral blood and bone marrow.

The prognosis depends on the underlying disease. In some cases, it is completely favorable.

Treatment of B_{12}-deficient anemia

- diet: limit fats, as they slow down hematopoiesis in the bone marrow. Increase the content of proteins in food, as well as vitamins and minerals.

- vitamin B_{12} in the form of cyancobalamin and oxycobalamin. These drugs differ in digestibility. Cyancobalamin is absorbed quickly. Oxycobalamin - more slowly.

Principles of therapy:

- saturate the body with vitamin

- supportive therapy
- prevention of the possible development of anemia.

Cyancobalamin is more often used in a daily dose of 500 micrograms (gamma). This dose is used if there are no complications (funicular myelosis, coma – in these cases, 1000 mcg of the drug per day is prescribed).

The drug is administered daily. There are various treatment schemes. Our experience shows that treatment at this dose for 20-25 days leads to a complete cure of B_{12}-deficient anemia. Further on, the patient is prescribed life-long maintenance therapy with vitamin in a dose of 500 mcg (1 injection) per month to prevent relapse of the disease.

If the cause of anemia is a helminthic invasion, etiotropic therapy is performed.

Before establishing a diagnosis, vitamin B_{12} should not be administered, since even one injection changes the picture of the bone marrow, which makes diagnosis difficult.

Criteria for evaluating the effectiveness of therapy:

- the most reliable marker of the effectiveness of the initiated treatment is a sharp reticulocytosis (the so-called reticulocytic crisis) after 5-6 injections, if it is not present, then there is a diagnostic error,
- complete recovery of blood parameters occurs after 1.5-2 months, and the elimination of neurological disorders - within six months.

The diagnosis of folic acid deficiency anemia is confirmed by the determination of the content of folic acid in blood serum and erythrocytes using microbiological methods. Treatment is carried out with folic acid preparations at a dose of 5-10 mg/day. Prevention of folic acid deficiency anemia should be carried out in pregnant women who are at risk of developing this deficiency at a dose of no more than 5mg per day.

HEMOLYTIC HEREDITARY MICROSPHEROCYTIC ANEMIA

Hemolytic hereditary microspherocytic anemia (familial hemolytic jaundice, Minkowski - Chauffard disease) is a form that occurs due to increased destruction of red blood cells and is accompanied by jaundice.

Etiology and pathogenesis of hemolytic hereditary microspherocytic anemia

The disease is based on a genetically determined anomaly in the membrane structure of erythrocytes, characterized by an irregular shape (spherocytosis). Such erythrocytes, due to reduced osmotic and mechanical resistance, undergo increased destruction mainly in spleen (intracellular hemolysis), as a result of which anemia, hemolytic jaundice, and spleen hyperplasia develop.

Clinical picture of hemolytic hereditary microspherocytic anemia

In the blood: signs of anemia of various intensity, high reticulocytosis, moderate neutrophilosis. Spherocytosis. The average diameter of red blood cells is less than 7.2-7 microns. The spherical index is less than 3. The minimum osmotic resistance of erythrocytes is reduced (0.7-0.6% at a norm of 0.48-0.44% NaCl), the maximum is increased (0.3-0.25% at a norm of 0.4-0.36% NaCl). Hyperbilirubinemia due to unconjugated bilirubin.

The picture of the bone marrow during crises is characterized by increased erythropoiesis. Coombs' test is negative. The course of the disease is chronic, wave-like: light intervals are replaced by hemolytic crises, frequent repetition of which can lead to depletion of the compensatory ability of the bone marrow with symptoms of aplasia or hypoplasia of hemopoiesis (aplastic crises). Relapses are often provoked by intercurrent diseases. The diagnosis is established on the basis of the clinical and hematological picture and family history (symptoms of hemolytic jaundice in family members).

Treatment of hemolytic hereditary microspherocytic anemia

The radical method of treatment is the removal of spleen, the main organ of blood destruction, after which clinical recovery occurs, although spherocytosis and reduced osmotic resistance of erythrocytes remain.

With rare and rapidly arrested hemolytic crises, indications for splenectomy are relative. Antianemic measures (blood transfusions, vitamin B_{12}, iron, corticosteroids) are ineffective and even contraindicated.

The prognosis is more often favorable. Death during an acute severe hemolytic crisis is a rather rare phenomenon.

HEMOLYTIC HEREDITARY NON-SPHEROCYTIC ANEMIA

Hemolytic hereditary non-spherocytic anemia (macrocytic) is a heredo-familial disease caused by the dominant inheritance of red blood cells inferiority (violation of various enzyme systems, glucose utilization), leading to accelerated destruction of the latter. The most common cause is a deficiency of glucose-6-phosphate dehydrogenase (G-6-PDG), pyruvate kinase, decreased content of reduced glutathione. With a deficiency of G-6-PDG, hemolytic crises can most often be provoked by drugs (sulfonamide preparations, nitrofuran derivatives, etc.).

Clinical picture of hemolytic hereditary non-spherocytic anemia

The clinical picture is very similar to that of congenital spherocytosis (anemia, reticulocytosis, bilirubinemia, jaundice, splenomegaly).

Diagnosis of hemolytic hereditary non-spherocytic anemia

The diagnosis is established on the basis of clinical and hematological data, macro- or normocytosis, normal osmotic resistance of erythrocytes, absence of spherocytosis, negative Coombs' test, detection of deficiency of these enzymes in erythrocytes.

Treatment of hemolytic hereditary non-spherocytic anemia

Treatment is symptomatic. Iron preparations, vitamin B_{12} are ineffective. With severe anemia, transfusions of erythrocyte mass are performed, corticosteroids are used. Splenectomy is ineffective. The prognosis is serious, especially with frequent hemolytic crises.

ACQUIRED HEMOLYTIC ANEMIA

Acquired hemolytic anemia is a symptom complex of polyetiological origin characterized by jaundice and anemia mainly due to intravascular hemolysis caused by external factors.

Under the influence of various factors (physical, chemical, medicinal, bacterial, parasitic, etc.), as a result of immunization of the body, anti-erythrocyte autoantibodies are produced that lead to increased hemolysis of erythrocytes. The phenomena of hemolysis are

aggravated by a secondary increase in the erythrophagocytic activity of the spleen.

Clinical picture of hemolytic acquired anemia

Characterized by violation of the general condition, weakness, headaches, jaundice of varying intensity, subfebrile body temperature, moderate enlargement of the spleen, sometimes liver. In the blood: signs of anemia of varying degrees, reticulocytosis. Osmotic resistance of erythrocytes is not changed or slightly increased. The diameter of red blood cells is normal. The course is chronic, however, acute severe hemolytic crises with high body temperature, signs of deep anemia, hemoglobinuria can be observed.

Diagnosis of hemolytic acquired anemia

The diagnosis is established on the basis of the clinical and hematological picture, the absence of pronounced spherocytosis and a positive Coombs' test (direct or indirect), indicating the presence of autoagglutinins.

Treatment of hemolytic acquired anemia

Corticosteroid hormones (prednisolone 0.5-1 mg/kg of body weight per day) are used, especially for hemolytic crises, according to vital indications - transfusion of one-group of individually compatible erythrocyte mass, strictly selected by a negative indirect Coombs' test. Splenectomy is indicated only in the absence of success after prolonged conservative therapy.

The prognosis is less favorable than in familial hemolytic jaundice. Relapses are possible. The criterion of recovery is the appearance of a negative Coombs' test.

APLASTIC ANEMIA

This disease was first described by Paul Ehrlich in 1888 in a 21-year-old woman. The term "aplastic anemia" was proposed by Chauffard in 1904. Aplastic anemia (AA) is one of the most severe disorders of hematopoiesis with a mortality rate exceeding 80%.

According to modern concepts, AA is understood as a disease that occurs as a result of damage to a blood stem cell, which results in a deep inhibition of hematopoiesis.

AA is a fairly rare disease; its frequency is 5 cases per 1 million population per year. AA is more common in young people, equally frequent in men and women.

Etiology and pathogenesis of aplastic anemia

AA is a polyetiological disease. The reason for the development of aplastic anemia can be an increased sensitivity to medication (idiosyncrasy). Reactions of this type are unpredictable and have no relationship between the dose of the drug and the duration of administration. The most common causes of AA are chloramphenicol (levomycetin), sulfonamides, tetracycline, streptomycin, butadione, gold compounds, barbiturates, bucarban, decaris, anti-thyroid and antihistamin preparations. The most severe AA is associated with taking levomycetin.

Among physical factors, it is necessary to highlight the effects of ionizing radiation. An increase in the frequency of AA cases was recorded in patients receiving radiation therapy for diseases of the bone and joint apparatus, as well as in roentgenologists and radiologists.

In some AA patients, the onset of the disease is associated with infectious diseases, such as viral hepatitis (A, B and C). In addition to hepatitis virus, AA can be caused by Epstein-Barr virus, cytomegalovirus, herpes virus, parvoviruses and human immunodeficiency virus (HIV). Often, the cause of AA remains unclear despite the most thorough examination of the patient and analysis of anamnestic data. In such cases it is said to be idiopathic aplastic anemia.

Mechanisms of AA development:

1. Internal defect of a blood stem cell.
2. Immune response to hematopoietic tissue.
3. Defect of the supporting function of the microenvironment.
4. Hereditary genetic defect.

Of these four factors, a leading role is assigned to a blood stem cell defect. This is confirmed by the association of AA with clonal bone marrow diseases, such as paroxysmal nocturnal hemoglobinuria, myelodysplastic syndrome and acute myeloblastic leukemia.

Discussing the role of immune reactions in the pathogenesis of AA, it should be noted that aplastic anemia cannot be regarded as a classic autoimmune disease. In AA, the immune system reaction is

most likely directed against the antigen (antigens) appearing on the cytoplasmic membrane of a blood stem cell as a result of a mutation in its genetic apparatus.

Clinical picture of aplastic anemia

The following syndromes are distinguished:

1. anemic
2. hemorrhagic
3. syndrome of infectious complications

Upon examination, the patient reveals pallor of the skin and mucous membranes, manifestations of hemorrhagic diathesis in the form of punctate hemorrhage (petechial) and small bruises. Circulatory insufficiency associated with anemia can lead to appearance of edema in the lower extremities and to an increase in liver size.

Diagnosis of aplastic anemia

The picture of peripheral blood is represented by tricytopenia. The decrease in hemoglobin is significant and can reach a critical level of 20-30 g/l. The color index is usually equal to one, but in some cases, there may be hyperchromia and macrocytosis of erythrocytes. The number of reticulocytes is sharply reduced. Pronounced leukopenia (agranulocytosis) is characteristic. The absolute content of lymphocytes is not changed or reduced. The number of platelets is always reduced, in some cases it is not possible to detect them at all. In most cases, ESR increases (up to 40-60 mm/hour). The detection of bi- or tricytopenia in the study of peripheral blood serves as the basis for performing a morphological study of the bone marrow.

The diagnosis of AA is established on the basis of a typical histological picture of the bone marrow obtained by trepanobiopsy of the iliac crest. Histological examination of the bone marrow reveals a large amount of adipose tissue, the content of which can reach 90%. Stromal and lymphoid elements are found among the dominant adipose tissue. Hematogenic cells are extremely scarce: erythroid and granulocytic precursors are found in a small number. Megakaryocytes are absent.

Treatment of aplastic anemia

The treatment of AA is a very difficult task. The main and only pathogenetic method of treatment that allows to count on saving the patient's life is bone marrow transplantation from a compatible donor.

If it is impossible to find a donor, palliative therapy is performed. The immunodepressant cyclosporine A is used as a basic drug. In patients with non-severe AA, the use of this drug allows us to count on success in a number of cases. Glucocorticoids, androgens and anti-lymphocytic globulin can improve the state of hematopoiesis in patients with mild AA, but, however, an increased risk of subsequent development of clonal bone marrow diseases should be taken into account. The use of cyclosporine A minimizes this risk. It should also be noted that some patients with mild AA who have overcome the 6-month survival threshold may experience spontaneous improvement. All AA patients need replacement transfusion therapy with erythrocyte and/or platelet mass. In addition, antibacterial and mycostatic therapy is carried out in order to prevent or treat infectious complications.

THALASSEMIA

This is a group of hereditary diseases, which are based on a decrease in the production of alpha or beta chains of hemoglobin (normal hemoglobin consists of two alpha and two beta chains). The disease occurs among people from the Mediterranean, Africa, the Middle East, India and Southeast Asia.

Beta-thalassemia is caused by a violation of the production of beta chains of hemoglobin. Most clinical manifestations are caused by the alpha chains excess accumulation, which are extremely toxic to the cell. The deposition of alpha chains in the precursors of erythrocytes leads to a violation of their maturation and death in the bone marrow (ineffective erythropoiesis). Those red blood cells that are still formed are defective and are quickly destroyed by the spleen. The production of erythropoietin in response to anemia stimulates the bone marrow, which grows, deforming and destroying bones. Increased iron absorption and constant blood transfusions lead to hemosiderosis. The clinical classification of beta-thalassemia is based on the severity of the disease.

Alpha-thalassemia develops when the production of alpha chains of hemoglobin is disrupted. Due to the excess of beta chains, along with normal hemoglobin, there is formation of hemoglobin consisting of four beta chains (hemoglobin H). The presence of this hemoglobin

in the erythrocyte reduces its resistance to various damaging factors, as a result, hemolytic anemia develops. The alpha chains of hemoglobin are encoded by two pairs of genes; the clinical picture is determined by how many of them continue to function. A condition in which none of the genes are functioning is fatal, and the fetus dies in utero. If one gene is functioning, hemoglobinopathy H - hemolytic anemia develops, clinically similar to G-6-PDG deficiency. It should be kept in mind that hemoglobin H is functionally deficient, so measuring the level of hemoglobin gives an understated idea of the severity of anemia. If two or three genes function, the disease proceeds asymptomatically or with moderate anemia.

Treatment of thalassemia

With minor beta-thalassemia, treatment is not required, the same applies to alpha-thalassemia - with the exception of hemoglobinopathy H, in which it is necessary to avoid drugs that provoke hemolysis (in severe cases, splenectomy and transfusions of erythrocyte mass are also resorted to). The basis of the therapy of major beta-thalassemia consists of transfusions of erythrocyte mass, splenectomy and fighting against the consequences of these measures - hemosiderosis and infectious complications. Splenectomy eliminates the main focus of destruction of erythrocytes, which reduces the need for transfusions of erythrocyte mass.

Complexing agents. The ability of the body to remove iron is quite low, therefore, transfusions of erythrocyte mass lead to its accumulation in quantities many times exceeding the normal supply, that is, to hemosiderosis. Iron deposition in organs leads to heart failure, diabetes mellitus, hypogonadism, liver damage. Deferoxamine allows to avoid hemosiderosis. Bone marrow transplantation is associated with significant risk, but if successful, it leads to recovery. It is indicated for patients with major beta-thalassemia in the presence of a suitable donor.

HEMOBLASTOSES

Hemoblastoses are tumors from hematopoietic cells. When bone marrow is affected, they are referred to as leukemias. The division is conditional, since the tumor can leave the bone marrow intact and

spread in it only later. Since we are talking about a tumor that affects the bone marrow, the most common sign of leukemia is the suppression of hematopoiesis, and mainly of the germ to which the tumor cells belong.

Classification of hemoblastoses

All hemoblastoses are designated in accordance with the name of the cells reflecting their cytomorphological essence (acute myeloblastic leukemia, chronic lymphocytic leukemia, etc.). The traditional names of some hemoblastoses reflect the main syndrome of the disease (osteomyelosclerosis, macro-globulinemic hemoblastosis), and some of their types have a second name after the surname of the author who first described and studied them (Cesari, Waldenstrom, etc.).

Hemoblastoses can be benign and malignant.

There are the following 2 groups of hemoblastoses: leukemias and lymphomas. Leukemias are tumors from hematopoietic cells with primary localization in the bone marrow. Lymphomas are tumors from hematopoietic cells, which are characterized by extramedullary localization and focal tumor growth.

The existing classifications of leukemias are based on the separate stable properties of the cells that represent the leukemia: these are either the source cells of leukemia, or their more differentiated offspring. Leukemias are divided into 2 main groups, acute and chronic.

Etiology of leukemia

✓ The role of ionizing radiation. The frequency of acute leukemia among patients with spondylosis, whose spine had previously been irradiated for the purpose of anesthesia, is quite exemplary.

✓ The role of chemical mutagens. The possibility of increase in the incidence of leukemia among people exposed to benzene has been known for a long time.

✓ The role of viruses. To date, there is a lot of experimental material on the possible viral nature of leukemia in animals. In the course of experimental studies, viral oncogenes were identified - genes that can cause a cell to continuously proliferate after being embedded in its genome.

✓ The role of heredity. Leukemia can occur in families where there have been patients with leukemia of a similar form, genetic defects with or without changes in chromosomes have been registered.

ACUTE LEUKEMIA

The following types of acute leukemia (AL) are distinguished in accordance with the scheme of hematopoiesis.

1. Myeloid:
* myeloblastic;
* myelomonoblastic;
* monoblastic;
* promyelocytic acute leukemia.
* erythromyelosis
* megacarioblastic
2. Lymphoblastic: B- and T-cell.

Etiology and pathogenesis of leukemia

For AL, as for most other tumor diseases, a specific etiological factor has not been identified. However, there are several predisposing factors that significantly increase the risk of developing this disease:

- Congenital diseases with increased chromosomal instability (congenital agranulocytosis, Bloom, Klinefelter, Turner, Wiskott-Aldrich syndrome, Fanconi anemia, etc.). Thus, with Down syndrome (changes in the 21st pair of chromosomes), the probability of AL is 20 times higher than in a healthy population; with AML, translocation is also often determined;
- viruses are the cause of the development of adult T-cell leukemia/lymphoma; the role of viruses in the occurrence of leukemia in animals (cows, primates) has been proven; RNA retroviruses are of particular importance; Epstein-Barr DNA viruses participate in the oncogenesis of Burkitt lymphoma, a number of B-cell ALL and lymphomas associated with acquired immunodeficiency virus, however, there are no clear indications that viruses alone are the cause of tumor development;
- connection with ionizing radiation, as well as chemo- and radio-therapy for other tumors (10-13% of patients have secondary AML developing from 2 to 9 years, especially when using drugs such

as mustragen, procarbazine, chlorbutin, cyclophosphan, lomustine, teniposide, etoposide);

- tobacco smoking, especially in people over 60 years of age;
- benzene, which, after prolonged exposure of the body, gives a leukemogenic effect.

The natural incidence of leukemia is 120-150 cases a year per 1 million people, and there are two peaks of morbidity: at 3-4 years and at 60-69 years, men get sick more often than women.

According to the modern theory of hematopoiesis, the stem cell is the ancestral polypotent element of hematopoiesis. This is the 1st undifferentiated class of cells. A leukemic agent (virus, mutation) can affect one of the progenitor cells of hematopoiesis, which is the starting point for the formation of a clone of leukemic cells. More often, the mutation occurs at the level of the stem cell. When the mass of the tumor is about 10^{12} cells, clinical manifestation occurs.

Leukemia can successively go through different stages of progression, but sometimes the disease begins with symptoms that are characteristic of the final stage: suppression of normal hematopoiesis lineages, formation of tumor conglomerates from blast cells in different organs or resistance to regular cytostatic drugs.

Each stage of progression represents a qualitative change of cells, and often only a certain part of them.

So, tumor progression is a qualitative change in the behavior and morphology of tumor cells resulting from increased variability of their genetic apparatus, leading to the development of polyclones and the selection of the most autonomous subclones.

Acute Leukemia Clinic

Characteristic nonspecific symptoms of AL:

* general weakness, dizziness, cardiac manifestations of anemic syndrome (in elderly patients);
* fever, decreased appetite, weight loss;
* bleeding;
* infectious diseases;
* pain syndrome (ossalgia, arthralgia, myalgia).

Specific symptoms:

* lymphadenopathy, hepatosplenomegaly;
* gum hyperplasia;
* infiltration of the skin:

* severe hemorrhagic syndrome;

* neurological symptoms - neuroleukemia;

* hematological syndrome (anemia, thrombocytopenia, neutropenia)

An objective examination often reveals an increase in peripheral lymph nodes, liver, spleen, gum hyperplasia, skin infiltration, hemorrhagic syndrome of varying severity from petechial rashes to severe bleeding, neurological symptoms (meningeal signs, paresis of the facial nerve, oculomotor nerve, and other disorders). Three-stage cytopenia, anemia, or only leukopenia or leukocytosis can be detected in the blood.

The clinical picture consists of four main syndromes: hyperplastic, hemorrhagic, anemic and intoxication.

1. Manifestations of hyperplastic syndrome in acute leukemia are: moderate and painless enlargement of lymph nodes, liver and spleen, hyperplasia of the tonsils, with an increase in mediastinal lymph nodes shortness of breath develops.

2. Leukemic hyperplasia and infiltration of the bone marrow lead to inhibition of normal hematopoiesis, resulting in anemia and thrombocytopenia. 20% of patients have severe anemia (Hb level below 60 g/l, erythrocytes < 1-1.2*10^{12}/l, thrombocytopenia below 50*10^{9}/l), which indicates rapid progression of the process or delayed diagnosis.

3. Hemorrhages can be in the form of small-dotted or small-spotted solitary rashes on the skin and mucous membranes, or can manifest as extensive hemorrhages and profuse bleedings.

4. Intoxication syndrome is manifested by increasing weakness, increased fatigue, lethargy or, conversely, hyperexcitability, sleep disturbance, heaviness in the head, decreased appetite, tachycardia, increased body temperature.

Features of the clinical picture of various variants of leukemia:

Acute myeloid leukemia (AML):

* onset - more often with hematological disorders (anemia, leukocytosis with blasts, leukopenia with blasts, thrombocytopenia, sometimes thrombocytosis in the initial period),

* less often, the onset of the disease - with sore throat, fever,

* low intensity of extramedullary proliferation for a long time,

* localization of extramedullary proliferation, leukemic cells: lymph nodes, spleen, liver, testicles, ovaries, kidneys, lungs, meninges, skin.

Acute promyelocytic leukemia:

* hemorrhagic syndrome (malignant) - almost all patients die from intracerebral hemorrhage or gastrointestinal bleeding,
* hypofibrinogenemia
* severe intoxication
* liver, spleen, lymph nodes, as a rule, are not enlarged.

Acute monoblastic leukemia:

* necrotic changes of the pharynx, gums, internal organs
* pronounced malignancy of the course
* hepatomegaly
* lymphadenopathy
* specific skin lesion
* hemorrhages.

Acute erythroblastic leukemia:

* persistent severe anemia with a hemolytic component
* low severity of hyperplastic syndrome.

Acute lymphoblastic leukemia:

- splenomegaly,
- lymphadenopathy,
- ossalgia,
- neuroleukemia,
- leukemic infiltration of the testicles.

Acute leukemia is characterized by a staged course.

The first attack of the disease (acute period) is the stage of detailed clinical manifestations, the first acute period, covering the time from the first clinical symptoms of the disease to the effect of the initiated treatment (induction therapy).

Remission is the leveling of pathological manifestations of the process under the influence of anti-leukemia therapy. Complete remission is a complete normalization of clinical symptoms (lasting at least 1 month) analysis of bone marrow punctate and blood tests with the presence in the myelogram of no more than 5% of blast cells and no more than 30% of lymphocytes. Incomplete remission is the

normalization of clinical and hematological parameters, but blast cells remain in the bone marrow punctate (no more than 20%).

The relapse of the disease is caused by the return of the leukemic process to its previous indicators as a result of the release of the residual leukemic cell population from the controlling action of the therapy. Relapse is often characterized by clinical symptoms similar to the initial period of acute leukemia, but the intensity and speed of its development are more pronounced and have lower response to therapy.

Recovery is when persistent remission lasts for more than 5 years and anti-leukemia treatment can be stopped, but patients should be under life-long supervision of a hematologist.

The terminal stage is the final stage of tumor progression with complete depletion of normal hematopoiesis, resistance to cytostatic therapy and no chance of medical treatment effect. Such patients die.

Diagnostics

The list of diagnostic procedures that make it possible to diagnose acute leukemia:

1. Dynamic (weekly) blood examination (predominance of blast cells, presence of leukemic gaping (hiatus leukemicus)).

2. Sternal puncture (more than 20% of blast cells in the bone marrow, violation of normal cell ratios in the myelogram, reduction or absence of megakaryocytes) every 2-4 weeks.

3. Bone marrow examination obtained by trepan biopsy (diffuse or large-focal blast infiltration with violation of the normal ratio of hematopoiesis lineage, inhibition of normal hematopoiesis, bone resorption) - it should be repeated once in 2-3 months.

The blood picture in the advanced stage of acute leukemia is very characteristic. In addition to anemia (normal or hyperchromic, macrocytic) and thrombocytopenia, there are changes in the number of leukocytes in a fairly wide range: from $0.1*10^9$/l to $100*10^9$/l with a predominance of forms with normal and reduced leukopenic (38%) or subleukemic (44%) leukocyte count.

The cellular composition of the hemogram and myelogram is more often monomorphic, represented mainly by blast cells. Mature granulocytes are detected in the form of single stab and segmented neutrophils. There are almost no intermediate forms between blast cells and mature granulocytes, which reflects a failure in

hematopoiesis - leukemic gaping (hiatus leikemicus), characteristic of acute leukemia.

In non-lymphoblastic leukemias, immature granulocytes may be detected in peripheral blood: promyelocytes, myelocytes, metamyelocytes, slightly masking the phenomenon of leukemic gaping.

However, their number is small (usually no more than 10%), significantly less than in chronic myeloid leukemia.

20% of patients have aleukemic forms of the disease (absence of blast cells in the hemogram). However, in these cases, the composition of peripheral blood does not remain normal. As a rule, pancytopenia (anemia, thrombocytopenia, leukopenia) is observed, cellular ratios in the hemogram are violated, more often due to the predominance of lymphocytes. In such cases, bone marrow examination is of particular diagnostic value.

In trepanation, in acute leukemia, diffuse or large-focal infiltration of the bone marrow by blast elements is detected with a violation of the normal ratios of bone marrow hematopoiesis, an increase in the mass of active bone marrow, bone resorption and hemorrhage sites.

The criterion for the diagnosis of acute leukemia is a blast transformation of hematopoiesis. In the presence of 20% or more blast cells in the bone marrow, the diagnosis of acute leukemia is considered confirmed.

Cytochemical marker reactions play a certain role in the diagnosis of acute leukemia:

- positive reaction to sudan and peroxidase (acute myeloblastic leukemia);
- sharply positive reaction to nonspecific esterase (acute monoblastic leukemia);
- positive reaction to glycogen (acute lymphocytic leukemia).

Differential diagnosis of acute leukemia

They perform differential diagnosis of AL with the following diseases:

A. Agranulocytosis

B. Aplastic anemia

C. Nonspecific polyadenitis and connective tissue diseases, autoimmune diseases, autoaggressive hepatitis, acute hemolysis.

D. Viral infections, viral hepatitis, AIDS, infectious mononucleosis, virus-associated or reactive hemophagocytic syndrome

E. Infections — severe bacterial infections (sepsis), Hystoplasmacapsulatum, Mycobacterium tuberculosis (hematogenic disseminated tuberculosis), atypical mycrobacteria, Salmonallatuphi, Mycorspp., Brucellaspp. and Fuso-bacterimnecrophorum, Borrelia (Lyme disease), syphilis

Metastases of tumors in the bone marrow— neuroblastoma, small cell lung cancer, glandular cancer, etc.

F. Sarcoidosis

G. Hypereosinophilic syndrome

H. Other hemoblastoses

Treatment of acute leukemia

In acute leukemia, urgent hospitalization is indicated. General principles of treatment of acute leukemia:

1. Programmatic polychemotherapy.

- remission induction

- destruction of the leukemic clone

- reaching the level of blast cells in the bone marrow, according to the results of the myelogram, below 5%.

-consolidation of remission - with a decrease in blast cells according to the results of bone marrow puncture below 5%, it is necessary to consolidate remission with a more complete eradication (elimination) of leukemic cells and a restraining effect on the "dormant" leukemic subpopulation (residual disease)

-supportive chemotherapy - the final suppression of the leukemic clone due to months of cyclical use of polychemotherapy courses

2. Supportive therapy

- blood preparations

-antibiotics and their combinations

-antifungal drugs

3. Bone marrow transplantation.

4. Auxiliary methods: extracorporeal (leukapheresis, cytapheresis), substitution therapy, syndromic and symptomatic therapy.

The main method of treatment of acute leukemia is polychemotherapy - a certain combination of several cytostatic drugs that differ in the mechanism of action.

Principles of polychemotherapy:

1. shock method;
2. cyclicity;
3. intensity;
4. combination of cytostatic drugs.

All chemotherapeutics are divided into two main groups:

Group 1 is chemical agents that specifically act on the cell cycle (cyclospecific), acting in one or more phases of mitosis.

Group 2 are chemicals the action of which is independent of the cycle (non-cyclospecific).

Chemotherapy programs for acute lymphoblastic leukemia are highly complex and consist of alternating regimens with the use of prednisolone (or desamethasone) doxorubicin, L-asparaginase, cytarabine, cyclophosphane, methotrexate. As well as endolumbal administration of methotrexate, cytarabine, dexamethasone. The most commonly used is the "ALL -2009" protocol developed by the FGBI Hematology Research Center of the Ministry of Health of the Russian Federation, the Hoelzer protocol is also used. The entire treatment period, including induction, consolidation and supportive therapy included in this program, takes up to 3 years.

In the treatment of acute myeloid leukemia in Russia, the AML-01.10 protocol developed by the Hematology Research Center of the Ministry of Health of the Russian Federation is also widely used. In this protocol, a combination of cytarabine with doxorubicin is used (2 courses, and in the 2nd course cytarabine is administered continuously for 7 days) followed by a combination of cytarabine with idarubicin (3rd course) and mitoxantrone (4th course). This program involves continuous inpatient treatment for up to 110 - 130 days. Subsequent maintenance therapy takes up to 1.5 - 2 years (with interruptions).

Treatment of complications:

If there is a decrease in the level of erythrocytes, erythrocyte mass is injected, with a decrease in the level of platelets, platelet mass is injected, with a decrease in the level of leukocytes, colony-stimulating factors are used, in case of infection, antibiotic therapy is

prescribed: cephalosporins in combination with aminoglycosides, carbopenems, fluoroquinolone drugs, antifungal drugs.

The prognosis depends on the age of the patients. In acute lymphoblastic leukemia (ALL), the age from 5 to 10 years is prognostically favorable (persistent remission in almost 100% of cases), recovery in 80% of cases. In acute myeloblastic leukemia (AML) in patients under 60 years of age, remission is achieved in 75-85% of patients. Recovery occurs in 20% of patients. Each leukemia has its own chemotherapy programs. A big problem in treatment is "pretreatment", when, at the initial diagnosis in any therapeutic department, the patient is prescribed prednisolone, which forms subsequent resistance to all treatment programs.

Acute promyelocytic leukemia is one of the most severe types among acute leukemias, occurring acutely, sometimes rapidly. With proper treatment using transretinoic acid and cytarabine with daunorubicin, the recovery rate reaches 78%, but provided that unjustified therapy was not carried out at the preliminary stage. This form of acute leukemia is characterized by the development of DIC syndrome with fatal bleeding.

Table 1

Criteria for the effectiveness of therapy of acute leukemia.

The degree of manifestation of the therapeutic effect	Clinical status	Hemogram	Myelogram	Histological picture (trepanobiopt ate of the iliac bone)
Complete clinical and hematological remission	Normalization for at least 1 month.	Normalization	Normalization , blast cells no more than 5%	Blast cells are solitary or not detected
Incomplete clinical and hematological remission	Normalization	Normalization	Blast cells no more than 20%	Individual small focal clusters of blast cells
No therapeutic effect	Progression of clinical and hematological changes			

CHRONIC LEUKEMIA

There are two main types of chronic leukemia:

■ chronic myeloid leukemia;

■ chronic lymphatic leukemia.

In each form, a number of subforms are distinguished. Diseases are diagnosed by leukocytosis, unexplained by other causes.

■ Chronic myelosis (chronic myeloid leukemia) is neutrophilic leukocytosis in which cells are almost completely devoid of granularity. A slow increase in the spleen is observed in patients along with feeling healthy and no signs of intoxication.

■ Chronic lymphocytic leukemia is one of the most frequent leukemias of the elderly. In most cases, it is observed after 40 years, but sometimes at a young age. Chronic lymphocytic leukemia should be assumed in the presence of generalized lymphadenopathy and lymphatic leukocytosis in the blood test.

CHRONIC MYELOID LEUKEMIA

Chronic myeloid leukemia (CML) is characterized by clonal proliferation of premature stem cells, which leads to an increase in the number of granulocytes. Chronic myeloblastic leukemia, also called chronic myeloid or chronic myelocytic leukemia, is the most common type of leukemia. Every year, about 2,500 new cases of this disease are registered in Russia. Adults are more likely to have CML, about 2% of cases occur in children. CML is not a hereditary disease, but the disease is caused by a chromosomal disorder in bone marrow cells, called the Philadelphia chromosome, which leads to the formation of an excessive number of leukocytes.

Etiology and pathogenesis of chronic myeloid leukemia

Causes of CML development: chromosomal abnormality - the presence of the Philadelphia chromosome in leukemic cells. The Philadelphia chromosome is the result of a balanced translocation of the material between chromosomes 9 and 22. During this translocation, a proto-oncogene called abl is transferred from its usual position on chromosome 9 to a new location on chromosome 22, called bcr. As a result, a new chimeric bcr/abl gene is formed. The protein, a product of this chimeric gene, functions as tyrosine kinase

identical to the product of the abl gene, but with increased enzymatic activity.

Clinical picture of chronic myeloid leukemia

The symptoms of the disease usually develop slowly and include such manifestations as increased fatigue, unexplained weight loss, shortness of breath, pallor as a consequence of anemia. In most patients, the chronic phase is transformed into a phase that is less manageable and more painful for the patient. This second phase is called the "acceleration phase" and is characterized by an increase in the content of both mature and blast (immature) leukocytes in the blood stream. The third phase, the "blast crisis", is similar by its course to a very aggressive acute leukemia.

Clinical picture: splenomegaly, spleen infarctions, intoxication syndrome, weight loss, fever. In the terminal stage (the phase of rapid acceleration) - deep cytopenia, blast crises, ossalgia, spleen infarcts, lymph node sarcoma, leukemides, persistent fever.

Differential diagnosis is carried out with the following diseases: infectious mononucleosis, autoimmune hemolytic anemia, lymphogranulomatosis, leukemoid reactions of the lymphatic type.

The main causes of death are:

- infectious complications (75%),
- cardiovascular diseases (8-12%)
- the development of cancer (of skin, stomach, lungs) - 5-10%.

Prognostically unfavorable signs in CML:

- age of 60 years and older at the time of diagnosis;
- the number of blast cells in the blood is 3% and higher, in the bone marrow -5% and higher;
- the number of basophils in the blood is 7% and higher, in the bone marrow 3% and higher;
- platelet count - $700,0*10^9$/ l and higher;

Diagnosis of chronic myeloid leukemia

Hematological picture: hyperleukocytosis (from $15\text{-}20*10^9$/l to $800*10^9$/l), an increase in the number of granulocytes up to 85-95%, the appearance of immature granulocytes (metamyelocytes, myelocytes), basophilic-eosinophilic association, thrombocytosis up to $800*10^9$/l or more, lymphocytopenia.

The final diagnosis of CML requires bone marrow examination. The increased number of fully mature and immature leukocytes

(myelocytes and neutrophils) gives reason to suspect CML. Confirmation of the diagnosis is carried out by examining the bone marrow punctate and follows in the case of detection of cells containing Philadelphia chromosome.

Treatment of chronic myeloid leukemia

Upon confirmation of the diagnosis of CML, therapy with imatinib (tyrosine kinase inhibitor of the I generation) should be initiated. The initial dose is 400 mg per day. Treatment is carried out on an outpatient basis by daily taking of the drug, available in capsules of 100 mg or 400 mg. To assess the effectiveness of therapy, peripheral blood tests are monitored (after 3 months of treatment, the peripheral blood picture should be completely normalized), a cytogenetic study of the bone marrow (after 12 months, the Philadelphia chromosome is not to be determined) and the determination of the bcr-abl mRNA transcript (should be less than 0.1% after 18 months of treatment). If therapy fails, the dose of imatinib is increased to 600 mg and in case of further failure - to 800 mg. In the absence of full effect from the maximum dose, the patient is transferred to the inhibitors of tyrosine kinase of the second generation - nilotinib and dasatinib preparations.

Hematopoietic stem cell transplantation (HSCT) can cure a patient with CML. However, not every patient has a histocompatible donor. One way or another, the age and physical condition of the patient, the presence of a donor and the individual sensitivity to drugs shown in the first months of treatment - all these circumstances should be carefully weighed when making a decision on transplantation. Until recently, HSCT was mentioned in the context of bone marrow transplantation (BMT), since bone marrow was the only source of hematopoietic stem cells used in the treatment of patients. Stem cells are immature progenitor cells of hematopoiesis, subsequently developing into three types of blood cells: leukocytes, erythrocytes and platelets. Currently, stem cells are obtained from bone marrow, umbilical cord blood or peripheral blood of a donor. Whatever source is used, stem cells are injected into the patient's body after high-dose chemotherapy or radiation therapy designed to completely destroy the patient's leukemia cells.

Allogeneic transplantation requires the presence of a related or unrelated donor, histocompatible with the patient according to the

HLA system. A sibling usually acts as a related donor, but a donor can also be found among parents or other blood relatives (uncles, aunts, cousins). In any case, the attending physician begins the search for a compatible donor from the closest relatives and often performs typing of the patient's more distant relatives. If a suitable donor is not found, the doctor searches the database - the International Donor Registry. Regardless of whether a related or unrelated donor is found, the transplantation procedure is the same: the donor's stem cells are taken, which are then injected intravenously into the patient. Unlike autologous transplantation, donor cells are rarely frozen, since their infusion usually occurs within 24 hours after sampling.

In recent years, there have been reasonable assumptions about the possibility of treating CML in some patients with tyrosine kinase inhibitors. However, until the present, the only way to completely recover from CML is allogeneic bone marrow transplantation. Nevertheless, given the high risks of complications of this type of treatment, up to the lethal outcome, the time of its use is determined individually. Moreover, at least 85% of CML patients will survive at least (at least!) 10 years even in case of treatment with tyrosine kinase inhibitors of the I Generation alone.

CHRONIC LYMPHOCYTIC LEUKEMIA

Chronic lymphocytic leukemia (CLL) is a tumor disease of the lymphatic tissue of a monoclonal nature with a mandatory primary lesion of the bone marrow, represented by relatively mature lymphocytes (95% - B-lymphocytes, 5% - T-lymphocytes).

The disease is 2 times more common in men, affects the middle-aged and the elderly (50-70 years). The incidence of chronic lymphocytic leukemia in different countries ranges from 0.04 to 3.7 per 100,000 population. The average duration of the disease is 5-6 years, there are cases of both 2-3 year and 20-30 year course.

Etiology and pathogenesis of chronic lymphocytic leukemia

The etiology of chronic lymphocytic leukemia, like all hemoblastoses, has not been fully studied. The role of some mutagenic factors in the occurrence of chronic leukemia (chemical mutagenic factors, radiation, viruses) is known. Viral theory is widely discussed.

The Gross virus in mice, Moloney virus, Schwartz-Skulman virus in rats, causing chronic lymphocytic leukemia, were isolated. In 1982, a retro-virus was isolated from a patient with T-cell leukemia - human T-cell virus 1 (HTLV - 1). HTLV-2 was found in a patient with hairy-cell lymphocytic leukemia. The virus invades into the DNA of the host cell with the help of reverse transcriptase - the genetic code of the cell changes (mutation) - the cell becomes malignant.

As for the role of ionizing radiation, there was no increase in the number of cases of CLL in foci with increased radiation. Currently, it has been shown that, unlike other chronic leukemias, CLL is not induced by external factors. The hereditary genesis of some cases of CLL and the role of ethnic factors are described. There are both dominantly and recessively inherited cases. Cases of CLL in several members of the same family are described. There are numerous hereditary diseases that predispose to the occurrence of CLL, as they are associated with a defect in immunity.

With CLL, chromosomal abnormalities are often detected, more often in pairs 14, 11, 3, 18. There are a number of ethnic factors in the occurrence of CLL: in the USA, a large incidence is noted among Jews. The Kazakhs suffer from CLL much less often than the Russian population.

There is a mutation of one cell - more often a cell, the precursor of lymphopoiesis (B or T). Lymphoid proliferation occurs in the bone marrow, normal hematopoiesis is suppressed. The genesis of cytopenia in CLL is more often autoimmune, there are signs of autoimmune hemolytic anemia, thrombocytopenia. There is a dissemination of tumor cells from the bone marrow into the hematopoietic organs and other systems with further proliferation of lymphoid tissue in the lymph nodes, liver, spleen. Lymphocytic leukocytosis in the peripheral blood increases.

Clinic of chronic lymphocytic leukemia

Classification of chronic lymphocytic leukemia (according to Ray, 1975).

Stage 0. Lymphocytosis

Stage 1. Enlargement of lymph nodes.

Stage 2. The appearance of hepatosplenomegaly (possibly without lymphadenopathy).

Stage 3. The addition of anemia to previous syndromes.

Stage 4. Thrombocytopenia association.

According to the International System [Binet et al., 1981], chronic lymphocytic leukemia is divided into stages A, B and C. The first two stages correspond to the process spread over three (A) and more (B) lymphatic fields - lymph nodes of all peripheral groups, spleen, liver, and the third (C) - process with cytopenia (anemia, thrombocytopenia):

* A - Lymphocytosis in peripheral blood is more than 4×10^9/l, in red bone marrow - more than 40%. Hb 100 g/l, platelets more than 100.0×10^9/l; the spread of the process - up to two regions of enlarged lymph nodes (cervical, axillary, inguinal, liver, spleen).

* B – Hb more than 100 g/l, platelets more than 100×10^9/l, the spread of the process - more than three areas of enlarged lymph nodes.

* C - Hb less than 100 g/l and/or platelets less than 100.0×10^9/l, regardless of the regions of enlarged lymph nodes.

Clinical stages of chronic lymphocytic leukemia

* Initial stage. The detection of the disease is random, more often by changes in the general blood test. There may be complaints of a non-specific nature: general weakness, sweatiness, fatigue, decreased ability to work. Enlargement of one lymph node or a group of lymph nodes is possible- the lymph nodes are painless, elastic, mobile, not matted together. There is no enlargement of the liver and spleen. In the hemogram: more often, leukocytosis is moderate (20-40*10^9/l), due to lymphocytes (40-50%), while absolute lymphocytosis should be at least 5*10^9/l. Leukolysis cells appear in the blood, Botkin-Gumprecht shadows. In the bone marrow, the lymphoid lineage comprises at least 30% (30-40%) of cells, there is some narrowing of the erythroid and megakaryocytic lineages. The initial stage can last from 2 to 8 years or more.

* The expanded stage of CLL. There is further tumor growth, lymphoid proliferation. Generalized lymphadenopathy (GLAP), hepatosplenomegaly, weight loss and a tendency to infections often appear. The hemogram shows an increase in lymphocytic leukocytosis. The degree of leukocytosis can be different (50-800-900*10^9/l), a leukopenic variant rarely occurs. In the expanded stage, lymphocytes make up to 60-90% in peripheral blood, earlier forms (lymphoblasts, prolymphocytes) appear. Anemia, thrombocytopenia, Botkin-Gumprecht shadows are often detected. In the benign form, the

number of leukocytes increases slowly with long preservation of hematopoiesis. With a tumor form against the background of generalized lymphadenopathy, there is faster enlargement of one group of lymph nodes, but leukocytosis in this form is low. With the bone marrow (intramedullary) form, there is no pronounced hyperplastic syndrome, but severe anemia, thrombocytopenia appear earlier, lymphoid proliferation in the bone marrow increases faster.

* Terminal stage of CLL. Intoxication and cachexia are increasing. As a rule, severe cytopenia develops: anemia, thrombocytopenia, leukopenia. The addition of infections is characteristic. There may be a blast crisis (an increase in the number of lymphoblasts more than 20-30% in the bone marrow). More often, patients die not from a blast crisis, but from the addition of other more grave diseases that can appear in the expanded stage (lymphosarcomas, cancers - more often skin cancer, bronchogenic cancer).

Criteria of the remission stage

In the bone marrow, lymphocytes are no more than 30%, the remaining indicators are normal. In the hemogram - lymphocytes no more than 4 thousand, Hb more than 110 g/l (without blood transfusions). Reducing the size of the liver, spleen, and lymph nodes to normal.

Criteria for the progression of CLL: weight loss of more than 10% in 6 months, increasing weakness, sweatiness, an increase in body temperature, an increase or appearance of cytopenia, enlargement of spleen, an increase in the number of enlarged lymph nodes by half in 2-3 months, duplication of leukocytes in 6 months or an increase by 50% in 2 months.

Diagnosis of chronic lymphocytic leukemia

Diagnosis is carried out according to the algorithm for patients with lymphadenopathy and lymphocytic leukocytosis. As with other hemoblastoses, the diagnosis should be established on the basis of morphological studies of the bone marrow or lymph nodes.

Treatment of chronic lymphocytic leukemia

1. Combating the progression of the tumor process - primary containment therapy, course chemotherapy, supportive therapy.

2. Treatment of autoimmune hemolytic anemia - hormonal therapy, splenectomy.

3. Fighting infectious complications – antibiotics.
4. Stimulation of the body defenses – immunoglobulins.

Treatment of chronic lymphocytic leukemia in the initial stages is not carried out. The patient is under the supervision of a hematologist. The disease may not progress for many yearsor even decades.

At the beginning of progression, manifested by an increase in leukocytosis, moderate lymphadenopathy, leukeran (chlorambucil) is commonly prescribed (especially in elderly patients). 10-15 mg of the drug is prescribed daily. Leukocytosis in CLL under the influence of leukeran decreases slowly, often only after a total dose of 200-250 mg. In cases where the patient had anemia and thrombocytopenia, steroid hormones are prescribed simultaneously with leukeran (30-40 mg of prednisolone daily). The course of treatment is 1.5 - 2 months with a total dose of leukeran of 500-600 mg. When the effect occurs, maintenance doses are prescribed - 10 mg 1-2-3 times a week.

In the last 2 decades, there have been fundamental changes in the treatment of CLL, namely: the introduction into clinical practice of fludarabine (a purine base antagonist), rituximab (a monoclonal antibody against CD20+ lymphocytes), as well as the appearance of interest in the antitumor drug bendamustine, synthesized in Germany more than 30 years ago.

FCR Combination:

Day 1 rituximab 375 - 500 mg/m^2,

Days 2, 3 4 fludarabine 25 mg/m^2,

Days 2, 3 4 cyclophosphane 250 mg/m^2 is currently the "gold" standard in the treatment of patients with CLL. The frequency of the general response is 95%, complete remissions - 72%. Conducting 6 courses of FCR (the duration of the course is 4 days, the interval between courses is 28 days) causes long-term remission in patients that does not require maintenance therapy.

Combination of rituximab with bendamustine (RB):

Day 1 rituximab 375 - 500 mg/ m^2;

Days 1 and 2 ibendamustine 100 mg/ m^2

(6 courses with an interval of 28 days) also demonstrates good efficiency, noninferior to FCR.

Splenectomy is one of the methods of treatment of autoimmune cytopenia in chronic lymphocytic leukemia. Of particular importance

is the treatment of infectious complications. Recently, leucopheresis has been used to treat lymphocytic leukemia with high leukocytosis and cytopenia. Patients with chronic lymphocytic leukemia have been maintaining feeling of well-being and ability to work for many years.

Additional therapy:

- detoxification therapy, treatment of infectious complications according to general rules.

- Immunomodulatory therapy: the use of intravenous immunoglobulin.

MULTIPLE MYELOMA

Multiple myeloma (myeloma, Rustitsky-Kahler disease) is a lymphoproliferative disease, the morphological substrate of which is plasma cells producing monoclonal immunoglobulin - lg (paraprotein). Multiple myeloma (MM) - the 2nd most common tumor disease of the blood system - occurs on average with a frequency of 3-4 per 100 thousand people per year. Mostly elderly people are ill (the average age is 66 years), only 2-3% of patients are younger than 40 years.

Often diagnosis of MM is significantly difficult. In 66% of cases, the diagnosis is made at stage III of MM, which is associated with a severe general condition, a worse prognosis. There are times when the disease is detected after the development of irreversible organ damage (spinal cord compression or terminal stage of chronic renal failure - CRF). Late diagnosis is due to the significant variability of clinical and laboratory signs, the need to use special laboratory tests to verify diagnosis, the lack of regular follow-up, as well as insufficient awareness of doctors about this disease. Depending on the leading clinical and laboratory symptoms, a patient with MM may first seek medical advice from a therapist, neurologist, nephrologist, rheumatologist, traumatologist. In the clinical picture of MM, several main syndromes are distinguished, the development of which is based on the biological features of tumor plasma cells.

Clinical picture of myeloma

Protein pathology syndrome. The most important link in the pathogenesis of MM is the ability of tumor cells to secrete monoclonal Ig and/or its fragments - light chains (Bence-Jones protein). More

often, in 55-66% of cases, monoclonal IgG is secreted, less often - IgA (20-25%). In 12-20% of MM patients, secretion of only light chains is detected (Bence-Jones myeloma). The secretion of monoclonal Ig of other classes (IgD, IgE, IgM) is extremely rare. In 1-4% of cases, there is no secretion. In 22-25% of patients, in addition to serum paraprotein, Bence-Jones protein is detected in the urine. Unlike normal Ig, which are antibodies and provide humoral immunity, monoclonal Ig is immunologically inactive. In addition, paraprotein (more often - light chains) can be deposited in various organs, mainly in the kidneys, leading to violation of their functions. With MM, the content of normal Ig decreases, which is accompanied by frequent bacterial infections of the respiratory and urinary tract. In addition to humoral immunodeficiency, in MM violations of the cellular component of the immune system are detected, therefore, infections caused by the herpes virus often develop.

Such clinical manifestations of the disease as nephropathy with the development of acute renal failure or chronic renal failure (CRF), hyper viscosity syndrome, polyneuropathy are associated with paraprotein secretion.

The occurrence of nephropathy is mainly caused by monoclonal light chains, much less often other types of Ig. Kidney damage in MM may have a different character. Cylindrical nephropathy develops most often (in 40-60% of cases), amyloidosis is detected less often (in 5-20%), the disease of light chain deposits is found in 5-10% of patients. Other variants of kidney damage are also possible (chronic tubulointerstitial nephritis, crystalline nephropathy, fibrillar glomerulonephritis), but they are quite rare. Kidney damage leads to the development of renal insufficiency, observed in 20-30% of patients at the time of onset of the disease and in 50% of patients as it progresses. Renal insufficiency in MM can be acute, reversible during treatment, and chronic, i.e. irreversible. In 10% of cases, MM starts with severe renal insufficiency, which requires hemodialysis.

The production of monoclonal protein in MM can lead to an increase in plasma viscosity (2-6% of cases). As a rule, significant hyperproteinemia is detected (IgG content>40 g/l, IgA>6 g/l), an increase in viscosity is also possible with a lower paraprotein content due to the ability of these proteins to polymerize. Clinically, the syndrome of increased viscosity is manifested by bleeding (nasal,

gingival bleeding), retinopathy with hemorrhage and violation of peripheral circulation (paresthesia, Raynaud's syndrome). Neurological disorders are typical: drowsiness, headache, dizziness, ataxia, diplopia. In severe, usually neglected cases, paraproteinemic coma may develop.

Signs of peripheral polyneuropathy of varying degrees are detected in 53% of MM patients. However, only in 5-10% of cases they are accompanied by pronounced sensory disturbances, muscle weakness, numbness and pain in the extremities.

Osteodestructive syndrome. Plasma cells, as well as stromal bone marrow cells, produce a number of cytokines during MM, which increase the activity of osteoclasts. The process of bone remodeling is disrupted, which leads to osteoporosis, foci of destruction and pathological fractures. Pain in the bones of the skeleton - the leading symptom in MM -is observed in 60-80% of cases. More often, the pain is localized in the lumbar spine, ribs. Often, patients are treated for a long time by a neurologist with an erroneous diagnosis of osteochondrosis or intercostal neuralgia. As a rule, flat bones (skull, vertebral column, ribs, collarbones, shoulder blades, pelvic bones) are affected, as well as metaphyses of tubular bones.

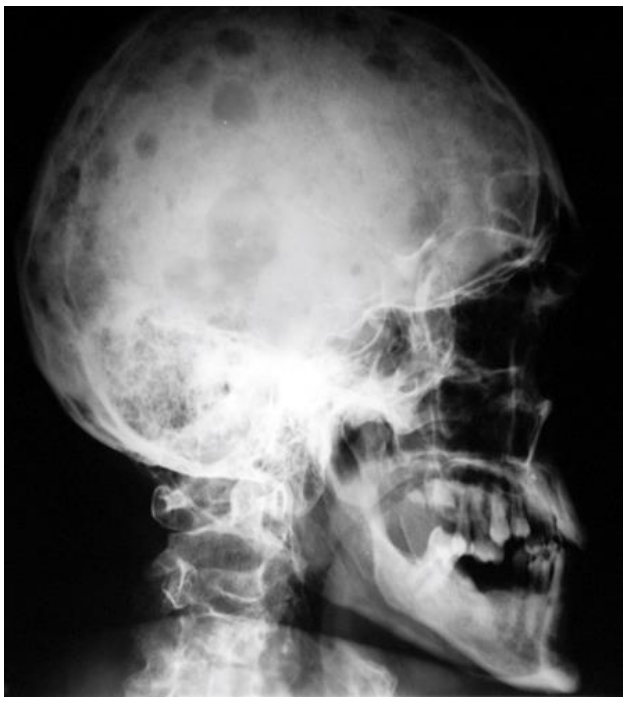


Fig. 9. Multiple pathological fractures of tubular bones in a patient with multiple myeloma.

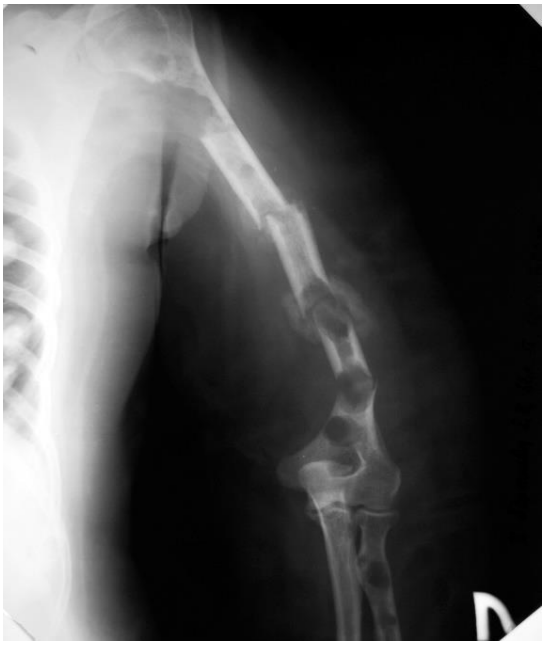


Fig.10. Changes in the bones of the skull in a patient with multiple myeloma

Radiologically, osteoporosis, foci of destruction, compression of vertebrae, pathological fractures are detected. 10% of patients develop spinal cord compression syndrome with lower paraparesis or paraplegia. Computer and magnetic resonance tomography are more sensitive than radiography, methods for diagnosing skeletal lesions and detecting tumor invasion beyond the bone.

Massive osteolytic syndrome can lead to hypercalcemia, observed in 20-40% of patients. Clinically, hypercalcemia is manifested by loss of appetite, nausea, vomiting, constipation, drowsiness, in severe cases - impaired consciousness. Hypercalcemia may be the cause of acute renal failure due to vasoconstriction of afferent arterioles in the glomeruli. An ECG reveals a broadening of the QRS complex and the T wave, a shortening of the QT and ST interval, and a slowdown in atrioventricular conduction.

With an aggressive course of MM, soft-tissue tumors may appear, more often due to the invasion of the cortical layer of bone. In rare cases, there is a tumor lesion of internal organs.

10-15% of MM patients develop AL-amyloidosis. With it, organs with high content of collagen (tendons, heart, tongue, blood vessels) are involved in the pathological process, and damage to the liver, kidneys, and peripheral nervous system is also possible. Often,

clinical manifestations caused by AL-amyloidosis dominate the clinical picture of MM. Systemic damage is more often observed, less often they detect individual organs damage:

* when amyloid is deposited in the glomeruli of the kidney, nephrotic syndrome develops.

* congestive heart failure, rhythm and conduction disorders.

* damage to the peripheral and autonomic nervous system - paresthesia, sensitivity disorders, muscle weakness, orthostatic hypotension, impotence, impaired motility of the gastrointestinal tract, emptying of the bladder, anhidrosis, carpal tunnel syndrome.

* macroglossia, hepatomegaly.

* progressive cachexia.

* hemorrhagic syndrome - increased fragility of blood vessels as a result of amyloid deposition in the endothelium, as well as a relative deficiency of coagulation factors adsorbed by amyloid.

Diagnosis of multiple myeloma

The complex of examination of MM patients includes the following laboratory and instrumental studies:

- complete clinical blood test, ESR;

- biochemical study of blood serum with assessment of: total protein and protein fractions (electrophoresis), urea, creatinine, uric acid, calcium, phosphorus, sodium, potassium;

- determination of daily protein loss in urine, electrophoresis of urine proteins;

- general urinalysis, determination of the Bence-Jones protein;

- determination of creatinine clearance;

- prothrombin time, activated partial thromboplastin time (APTT) (if necessary – expanded coagulogram);

- determination of pathological protein in blood serum and urine by immunofixation;

- quantitative assessment of the level of immunoglobulins and light chains (κ and λ) in blood serum and urine;

- X-ray examination of all flat bones and epiphyses of large tubular bones, computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography with 18-fluorodeoxyglucose (PET) of bones, bone densitometry in diffuse osteoporosis;

- aspiration biopsy of the bone marrow, trepanobiopsy of the bone marrow;

- CRP, β2-microglobulin, interleukin 6, lactate dehydrogenase (LDH) in blood serum;

- cytogenetic study of bone marrow cells (if possible, FISH-study (fluorescent in situ hybridization) and molecular genetic research methods to identify the rearrangement of genes responsible for the synthesis of immunoglobulins);

- immunophenotyping of blood and bone marrow cells in order to detect monoclonal B lymphocytes (plasma cell precursors) circulating in the blood or monoclonal plasma cells in the bone marrow with CD38+, CD19-, CD138+ phenotype.

- determination of heat shock proteins (Hsp90, Hsp70);

- biopsy of the oral mucosa, rectum, kidney in case of suspected amyloidosis.

A picture of blood. In 73% of cases, anemic syndrome is detected at the onset of MM, in all patients anemia develops as the disease progresses. Causes of anemia in MM:

* displacement of erythroid progenitor cells by tumor cells;

* reduction of erythropoietin synthesis;

* reduced sensitivity of erythroid lineage cells to proliferative signals;

* decrease in the lifetime of red blood cells,

* hemodilution.

In many ways, these processes are mediated by inflammatory cytokines. An important laboratory sign of MM is an increase in ESR. However, with the secretion of only light chains (Bence-Jones myeloma), a low level of monoclonal Ig secretion, as well as the presence of cryoglobulins, ESR remains low. Sometimes moderate thrombocytopenia, monocytosis are detected. The presence of plasma cells in the blood test does not indicate MM as it is, but with a confirmed diagnosis, the appearance of high peripheral plasmacytosis indicates a poor prognosis.

Thus, the clinical and laboratory signs of MM are very diverse, which leads to a large number of errors and late diagnosis of the disease.

MM should be excluded in the following cases:

* Newly detected proteinuria or renal insufficiency;

* Anemia or increased ESR of unknown origin;

* Detection of M-gradient during electrophoresis of serum or urine proteins;

* Ostealgia (especially with sciatica) in combination with changes in blood or urine tests;

* Detection of osteolysis foci during radiography of skeletal bones;

* Polyneuropathies of unclear genesis.

Forms of multiple myeloma

Nonsecretory multiple myeloma is observed in 1% of patients and is characterized by the absence of M-protein in blood serum and urine. The diagnosis is established on the basis of detection of ≥ 30% of plasma cells in the bone marrow, detection of target organ damage, secretion of monoclonal immunoglobulin in plasma cells by immunofluorescence technique. In patients with this form of the disease, hypogammaglobulinemia is detected in more than 60% of cases. The prognosis of the disease and the principles of medical tactics in this form of MM do not differ from the general group.

Osteosclerotic form of multiple myeloma, when the radiographic examination of bones reveals foci of osteosclerosis, is extremely rare. Osteolytic lesions of bone tissue in MM patients can be combined with foci of osteosclerosis, reflecting the processes of bone tissue reparation. In this case, we can speak about a mixed (osteolytic and osteosclerotic) type of lesion. Specifics of clinical manifestations in patients with osteosclerotic MM is the more frequent development of sensorimotor polyneuropathy, which occurs in 30-50% of patients. In classical MM, polyneuropathy is observed only in 1-8% of patients, although against the background of ongoing treatment with the use of the VAD program, velcade, revlimid, thalidomide, the frequency of neuropathy detection may increase. Isolated osteosclerotic type of bone tissue lesion occurs in 47% of cases with the so-called POEMS syndrome. The acronym POEMS is composed of the first letters of the following syndromes: *polyneuropathy, organomegaly or lymphadenopathy, endocrinopathy, M-protein and/or plasma cell dyscrasia, skin changes*. The cause of the POEMS syndrome is unclear.

Only in 5-20% of patients with POEMS syndrome, the number of plasma cells in the bone marrow exceeds 10%, which indicates that

the genesis of this disease is not always associated with multiple myeloma. The overall 20-year survival rate of patients is 50%. It is believed that MM in patients with POEMS syndrome proceeds favorably and is not the cause of death of patients. Chemotherapy for this disease, as a rule, is not carried out. For ostealgia, local radiation therapy can be used.

Criteria for the diagnosis of myeloma

Diagnostic criteria for multiple myeloma (the presence of all the three criteria is required).

1. Monoclonal plasma cells in bone marrow aspirate ≥10% or the presence of plasmacytoma proven by biopsy.

2. The presence of monoclonal protein in serum or urine. If the monoclonal protein is not detected (nonsecreting myeloma), ≥ 30% of plasma cells and/or the presence of a plasmocytoma are required for diagnosis)

3. Myeloma-related organ dysfunctions (1 or more):

- Hypercalcemia >10.5 mg/l or the upper limit of the norm;
- Renal insufficiency with serum creatinine level > 2 mg/dl;
- Anemia with hemoglobin levels less than 100 g/l or 20 g/l below normal;
- Lytic bone lesions or osteoporosis (if the patient has diffuse osteoporosis without foci of destruction in the bones or solitary plasmacytoma, then ≥ 30% of plasma cells in the bone marrow aspirate are required for diagnosis).

Currently, it is customary to distinguish smoldering (sluggish, asymptomatic) MM and MM with clinical symptoms (active). The diagnosis of smoldering MM is made on the basis of:

* The presence of more than 10% of plasma cells in the myelogram;

* Monoclonal Ig during electrophoresis (in serum IgG>30g/l, IgA>20g/l, Bence-Jones protein level in urine >1g/day.);

* Absence of organ damage caused by MM.

In patients with asymptomatic MM chemotherapy is not indicated. Careful monitoring is recommended with the repetition of laboratory tests every 3-4 months.

The diagnosis of active MM is made in the presence of:

* Monoclonal Ig in blood serum and (or) urine;

* Clonal plasma cells in the bone marrow and (or) confirmed clonal plasma infiltration in the biopsy sample of the affected tissue;

At least 1 of the following signs (other causes of these symptoms should be excluded):

- ✓ Hypercalcemia (serum Ca level >2.65 mmol/L);
- ✓ Renal insufficiency (blood creatinine> 177 mmol/L)
- ✓ Anemia (hemoglobin < 100 g/l);
- ✓ Bone damage (lytic foci or osteopenia);
- ✓ Frequent bacterial infections (more than 2 episodes in the last 12 months) associated with a decrease in normal Ig;
- ✓ Syndrome of increased plasma viscosity.

Quite often, 1-2% of people over 50 years of age are diagnosed with monoclonal lg in the absence of clinical signs of any disease. Such a phenomenon is referred to as monoclonal gammopathy of unclear genesis. Along with this, the M-gradient can be associated with other diseases (cancer of solid organs, diffuse connective tissue diseases, rheumatoid arthritis, chronic hepatitis, cirrhosis of the liver, etc.) Sometimes MM has to be differentiated with reactive bone marrow plasmacytosis that develop in various conditions (generalized viral infections, solid tumors, autoimmune diseases, etc.). In reactive plasmacytosis, there is no secretion of monoclonal Ig; in some cases, immunophenotyping of plasma cells is necessary to exclude their tumor origin.

Treatment and prognosis for myeloma

MM refers to non-curable diseases, i.e. it is impossible to cure MM completely. The life expectancy of patients depends on many factors related to the biological features of the tumor, the complications that have developed, and the treatment being carried out. On average, survival rate varies from 29 to 62 months.

Currently, there is no single concept for the treatment of multiple myeloma. Conditionally, two approaches to treatment can be distinguished: moderate chemotherapy and intensive chemotherapy with subsequent transplantation of autologous or allogeneic hematopoietic stem cells and the use of new drugs in the complex treatment: inhibitors of angiogenesis, proteasome inhibitors).

Modern MM therapy includes cytostatic preparations, radiation therapy, supportive treatment, orthopedic correction.

1. Chemotherapy is the basic treatment of MM. Alkylating drugs (melphalan or alkeran) are used in combination with prednisolone, as intermittent therapy, and in stage I treatment is not used, in stage II treatment is carried out in short shock courses, in stage III prolonged courses of chemotherapy can be used. In case of insufficient effectiveness, polychemotherapy is used: courses M2, VAD.

In recent years, targeted therapy drugs have appeared: proteasome inhibitors: bortezomib, carfilzomib and immuno-modulating drugs (thalidomide, lenalidomide). Bortezomib (velcade) is used as the first line of therapy, both in primary MM patients and in relapse of the disease.

Lenalidomide (revlimide) has pronounced immunomodulatory activity and inhibits angiogenesis. Both of the above indicated drugs are used in combination with dexamethasone, (VD and RD courses), as well as together (RVD courses). Very often bortezomib is used in combination with dexamethasone and cyclophosphamide (VCD), with dexamethasone and doxorubicin (PAD).

2. Radiation therapy at a dose of 40-50 Gy per lesion focus is carried out on the foci of osteolysis with the threat of fracture in the supporting parts of the skeleton, the zone of pathological fracture, local plasmocytic growth, symptomatic analgesic radiation therapy. Radiation therapy and chemotherapy are often combined, at that MM is considered a very radiosensitive tumor.

3. Surgical interventions are performed to remove an extramedullary growing tumor: decompression laminectomy. Fixing operations. Implantation of prosthetic vertebrae.

4. Maintenance therapy: erythrocyte mass, platelet concentrate. The most important treatment of hypercalcemia is chemotherapy, saline infusion, high doses of glucocorticoids (inhibit osteoclasts) with calcitonin, the use of biphosphonates (clodronate). Plasmapheresis is the therapy of choice for hyperviscosity syndrome. In case of renal insufficiency, program hemodialysis is used.

Infectious complications should be treated taking into account the sensitivity of flora to antibiotics. Intravenous introduction of immunoglobulin G to the most common bacterial infections is of preventive importance.

In the last 30 years, life duration of MM patients has increased by 2-3 times. Nevertheless, the disease still remains incurable. The most widespread is high-dose therapy with melphalan with transplantation of autologous hematopoietic tissue. In comparison with standard therapy, the percentage of complete remissions of the disease reaches 38% versus 14%. The overall five-year survival rate is 52% versus 12%. This therapy is successfully carried out in patients younger than 65 years.

High-dose chemotherapy with allogeneic bone marrow transplantation proved to be a highly effective method of treating MM (73% of complete remissions are observed, 6-year survival in the group of complete remissions reaches 50%). This method can be used only in the treatment of patients younger than 50 years due to the difficulties of selecting a related donor and high (up to 50%) toxic mortality associated with the development of the “graft versus host” syndrome, infectious and hemorrhagic complications due to longer myelosuppression. In reality, allogeneic transplantation can be performed in 5-10% of MM patients.

To relieve pain, nonsteroidal anti-inflammatory drugs are prescribed. With massive foci of osteolysis in long bones, local radiation therapy is justified if the diameter of the lesion is more than 1/3 of the diameter of the bone or if there are significant lesions of the cortical layer of the bone and the risk of developing pathological fractures is high.

In case of pathological fractures of long tubular bones, a good reposition and fixation of fragments is necessary. If fractures occur in places of large tumor nodes with a large diastasis of fragments, osteosynthesis is performed. For compression fractures of the vertebrae accompanied by radicular syndrome, chemotherapy drugs and analgesics are used. Wearing a corset is indicated in rare cases.

Currently, there is a new possibility of treating bone lesions in MM, which is associated with the widespread introduction of biphosphonates into clinical practice - a new class of synthetic drugs that are analogues of pyrophosphates. The action of biphosphonates is based on their ability to suppress the activity of osteoclasts, shorten their lifespan, and prevent the maturation of osteoclast precursors. In MM, such biphosphonates as bonefos (clodronate), bodronate

(ibadronate) are used both to prevent the progression of bone lesions and to combat hypercalcemia.

The main treatment for hypercalcemia is chemotherapy, including high-dose glucocorticoids. Hydration plays an important role in the treatment of this complication. With a mild degree of hypercalcemia (the calcium level is 2.6-3.5 mmol/l), the patient should drink up to 3 liters of mineral water with a low calcium content per day. In the toxic form of hypercalcemia, it is recommended to inject intravenously from 2-3 to 5 liters of isotonic sodium chloride solution and force diuresis by intravenous administration of furosemide.

With spinal cord compression and confirmation of its tumor nature, one of the main methods of treatment is local radiation therapy. There is no single opinion in the literature about which total focal dose is optimal. A number of researchers insist on a dose of 50 Gy or more, other authors consider a dose of 30-35 Gy sufficient, since there are much fewer delayed complications.

In the process of treating patients with MM, special attention is paid to the prevention and treatment of renal insufficiency. In order to timely prevent the development of acute renal insufficiency, treatment of hypercalcemia, indication of allopurinol during the first courses of chemotherapy, especially with a large tumor mass, as well as treatment of urinary infection, refusal to use nephrotoxic drugs (aminoglycosides) are necessary.

The main methods of treatment of already developed renal insufficiency are adequate chemotherapy and hydration. It should be taken into account that melphalan is not a nephrotoxic drug, but for patients with MM suffering from renal insufficiency it should be prescribed in a reduced dose due to an increased risk of myelosuppression associated with impaired excretion of this drug. Renal failure can be reversible with adequate hydration and chemotherapy. In severe uremia, hemodialysis is indicated. A number of authors suggest using plasmapheresis for the treatment of renal insufficiency.

Plasmapheresis is also used for hyperviscosity syndrome and bleeding with hyperproteinemia above 130–140 g/l. The absolute indication for plasmapheresis is paraproteinemic coma.

Anemia develops in most patients with multiple myeloma. With successful chemotherapy, anemia is usually stopped, but improvement

occurs after several courses of treatment as the tumor mass decreases and kidney function improves. With profound anemia, transfusions of erythrocyte mass are necessary to improve the quality of life of patients. Maintaining hemoglobin at a level above 100 g/l is especially important for elderly patients and patients with cardiovascular diseases. In recent years, erythropoietin has been used to treat patients with MM who have developed anemia. Recombinant erythropoietin is effective in 60-65% of patients with myeloma. It is prescribed at a dose of 150-200 IU/kg per day 3 times a week. A necessary condition for successful treatment is a low level of endogenous erythropoietin in the blood serum and adequate compensation for iron deficiency, which is intensively consumed during stimulation of erythropoiesis. The use of erythropoietin helps avoid complications of transfusion therapy.

Profound thrombocytopenia and granulocytopenia in the diagnosis of MM are rare and, as a rule, indicate pronounced infiltration of the bone marrow by plasma cells. In this case, it is not recommended to reduce the doses of chemotherapy drugs during induction treatment. However, adequate chemotherapy in such situation is possible only with appropriate accompanying therapy, including colony-stimulating factors G-CSF, GM-CSF and component hemoreplacement therapy.

Treatment of infectious complications is carried out according to the general rules for the treatment of patients with immunodeficiency, taking into account the data of bacteriological studies of blood, urine and sputum. With an increase in body temperature, the patient should be immediately hospitalized to begin antibacterial therapy, in which nephrotoxic drugs should be excluded. Since any infection in MM patients can lead to the development of acute renal failure, intravenous administration of isotonic sodium chloride solution, hemodez, as well as plentiful drinking is necessary.

In order to prevent infectious complications, immunoglobulin preparations for intravenous administration are used at a dose of 10 g every 3-4 weeks or 0.4 g/kg monthly, which reduces the frequency of infections and the severity of their course.

Treatment of MM is complex, but the leading place in it belongs to chemotherapy. The goal of chemotherapy at MM is to reduce the tumor clone as much as possible. There are 2 principal approaches in

the treatment of MM patients: standard chemotherapy and high-dose chemotherapy with peripheral stem cell transplantation (autologous bone marrow transplantation – autoBMT). Currently, autoBMT is the preferred method of treatment in MM patients younger than 60 years in the absence of severe concomitant diseases and achieving a good response after induction therapy. In these cases, the survival rate for 7 years is 80%. Patients who have contraindications to intensive treatment are given standard chemotherapy with the use of melphalan and prednisolone. In recent years, new drugs for the treatment of MM (bortezomib, thalidomide, lenalidomide) have appeared. Their use as part of chemotherapy regimens allowed to improve the results of treatment (an increase in the frequency and depth of remissions). Some studies indicate an increase in overall survival even with the use of these chemotherapeutic drugs.

The first approach to the treatment of multiple myeloma is based on the most cautious attitude to therapy, wait-and-see tactics, the use of low doses of alkylating drugs (melphalan, cyclophosphamide) and / or glucocorticoids (dexamethasone, prednisolone) in order to constrain tumor proliferation, improve the quality of life. Proponents of this approach to treatment believe that achieving complete remission and cure in multiple myeloma is practically impossible, and aggressive therapy can lead to a more aggressive course of the disease, deterioration of quality of life without a significant increase in relapse-free survival rate and total life expectancy of the patient. The main goal of this treatment is aimed at achieving a therapeutic plateau (stabilization of the disease, achievement of partial or unconfirmed complete remission, complete remission in rare cases). Moderate-intensity chemotherapy is indicated for patients older than 65-70 years or patients who, for some reason, cannot receive intensive chemotherapy with or without hematopoietic stem cell transplantation.

For the last 30 years, the traditional and standard first-line therapy of this group of MM patients has been a combination of alkeran (melphalan) and prednisolone (MP scheme). A positive clinical response to therapy under the MP program is noted in 50-60% of patients with multiple myeloma, but complete remission is achieved in 0-3% of patients. The overall survival rate of MM patients receiving MP therapy is 29 months on average. Cyclophosphamide can also be used as an alternative to alkeran. Cyclophosphamide

therapy is performed either as monotherapy or in combination with prednisolone.

The use of various regimens of polychemotherapy or high doses of dexamethasone increases the frequency of achieving complete remissions and responses to therapy in MM patients, but does not significantly affect the overall and relapse-free survival rates if hematopoietic stem cell transplantation is not used as a step of treatment. In this regard, polychemotherapy is of fundamental importance when preparing a patient for hematopoietic stem cell transplantation (HSCT). Long-term therapy with alkylating drugs in the pretransplantation period worsens the quality of autologous graft and reduces the effectiveness of HSCT. Polychemotherapy is also used as a second-line therapy in patients resistant to alkylating drugs or large doses of dexamethasone, as well as when it is impossible to clinically use large doses of glucocorticoid hormones.

Allogeneic hematopoietic stem cell transplantation may also be recommended as one of the methods of treatment of some MM patients. In recent years, it has been established that the therapeutic effect in MM patients is provided not only by the conditioning regime (high-dose chemotherapy and total or subtotal irradiation of the body), but also by the graft against leukemia (myeloma) reaction. This method of treatment can be indicated for MM patients younger than 55 years of age from the high-risk group who have an HLA-compatible relative donor. At the same time, factors such as the absence of cytomegalovirus carrier status in the donor and the recipient, the patient's somatic status, kidney function, and related diseases are taken into account.

About 80% of MM patients at the time of diagnosis have foci of osteodestruction in the bones or diffuse osteoporosis. Chemotherapy is of fundamental importance for the effective therapy of osteodestructive syndrome. Radiation therapy is used in the focal form of MM, plasmacytoma, severe pain syndrome, especially with compression of spinal cord roots, for the prevention and treatment of pathological fractures. Along with chemotherapy, therapy with biphosphonates is recommended for MM patients with bone damage, since their protective effect against the emergence of new foci of bone destruction has been proven. In clinical practice, pamidronate (Aredia), zoledronic acid (Zometa), clodronate (Bonefos) are used for

this purpose. Drugs such as Fosomax and Actonel in MM patients can only be used for the prevention of osteoporosis against the background of glucocorticoid therapy.

Replacement therapy with donor erythrocyte mass is carried out in patients with a hemoglobin level of less than 85 g/l. Considering that MM patients are mainly elderly people with concomitant diseases of the cardiovascular system, in some cases, for special indications, erythrocyte replacement therapy is performed in patients with a hemoglobin level of more than 85 g/l, but less than 110 g/l. Before starting treatment of anemic syndrome, such causes of anemia as deficiency of iron, vitamin B_{12}, folic acid are to be excluded. Successful chemotherapy is usually accompanied by a reduction and relief of anemia. Erythropoietin therapy is indicated for MM patients with anemia.

Prevention of uric acid nephropathy in MM patients is carried out with allopurinol at a dose of 300 mg/day and infusion therapy. Caution should be taken with alkalizing therapy in patients with hyperuricemia in combination with hypercalcemia. In this case, hypercalcemia is stopped first, and only after that sodium bicorbate is used. The presence of hypercalcemia in the patient requires active infusion therapy, the use of glucocorticoid drugs, and in severe cases, biphosphonates, among which intravenous administration of Zometa at a dose of 4 mg is most effective. With hyperviscosity syndrome, which usually occurs when the serum protein level is more than 100-110 g/l, plasmapheresis using blood cell separators is recommended.

Preventive antibacterial therapy is the first 3 months of MM treatment is most relevant. In case of the use of glucocorticoid drugs, MM patients must necessarily be prevented from fungal infection. The drug of choice in MM patients is fluconazole (diflucan), which has the lowest nephrotoxicity. In the case of an active infection, therapy is carried out taking into account the infectious agent and sensitivity of microflora to certain drugs.

APPENDIX A

Table 2

Normal myelogram (according to Sokolov V.V., Gribova I.A., 1972)

Indicators	Mean value, %	Limits of fluctuations, %
1	2	3
Reticular cells	0,9	0,1-1,6
Blasts	0,6	0,1-1,1
Myeloblasts	1,0	0,2-1,7
Neutrophilic: promyelocytes myelocytes metamyelocytes stab segmented	 2,5 9,6 11,5 18,2 18,6	 1,0-4,1 6,9-12,2 8,0-14,9 12,8-23,7 13,1-24,1
All neutrophilic elements	60,8	52,7-68,9
Eosinophils of all generations	3,2	0,5-5,8
Basophils	0,2	0-0,5
Erythroblasts	0,6	0,2-1,1
Pronormoblasts	0,6	0,1-1,2
Normoblasts: basophilic polychromatophilic oxyphilic	 3,0 12,9 3,2	 1,4-4,6 8,9-16,9 0,8-5,6
All erythroid elements	20,5	14,5-26,5
Monocytes	1,9	0,7-3,1
Lymphocytes	9,0	4,3-13,7

1	2	3
Plasma cells	0,9	0,1-1,8
The number of myelocaryocytes (in thousands in 1 μl)	118,4	41,6-195,2
Leuko-erythroblastic ratio	3,3	2,1-4,5
Erythrocaryocyte maturation index	0,8	0,7-0,9
Bone marrow index of neutrophils	0,7	0,5-0,9

APPENDIX B

HEMATOLOGY TESTS:

1. What is the name of the syndrome manifested by a decrease in the content of Hb per unit of blood volume?

a) polycythemia
b) erythrocytosis
c) anemia

2. An increase in the content of Hb in comparison with the upper limit of the norm occurs in all cases, except:

a) true polycythemia
b) the inhabitants of the highlands
c) pilots, after high-altitude flights
d) leukemia

3. Indicate the normal content of erythrocytes in peripheral blood in healthy men:

a) 4,0 - 5,0 * 10^{12}/L.
b) 3,9 - 4,7 * 10^{12}/L.
c) 3,0 - 4,0 * 10^{12}/L.
d) 5,0 - 6,0 * 10^{12}/L.

4. Indicate the normal content of red blood cells in healthy women:

a) 4,0 - 5,0 * 10^{12}/L.
b) 3,9 - 4,7 * 10^{12}/L.
c) 3,0 - 4,0 * 10^{12}/L.
d) 5,0 - 6,0 * 10^{12}/L.

5. The normal Hb content in men is:

a) 120 - 140 g/l
b) 130 - 160 g/l
c) 150 - 170 g/l

6. Hematocrit increase is characteristic of:

a) leukemia
b) anemia
c) compensatory erythrocytosis

7. In what type of anemia is there an increase in the color index over 1.05?

a) aplastic anemia
b) hemolytic anemia

c) normochromic anemia

d) B_{12}-deficiency anemia

e) iron deficiency anemia

8. What type of anemia is characterized by a decrease in the color index below 0.8?

a) aplastic anemia

b) hemolytic anemia

c) normochromic anemia

d) B_{12}-deficiency anemia

e) iron deficiency anemia

9. The normochromic nature of anemia is not observed in:

a) aplastic anemia

b) leukemia

c) chronic renal failure

d) B_{12}-deficiency anemia

10. The normochromic nature of anemia occurs in:

a) iron deficiency anemia

b) folate deficiency anemia

c) hemolytic anemia

d) chronic posthemorrhagic anemia

11. What kind of disease can you think about when a patient has a large, deep, painful hematoma in the right thigh area after a slight contusion:

a) hemorrhagic vasculitis

b) Werlhof's disease

c) hemophilia

d) Rendu-Osler disease

12. Hemoblastoses are characterized by all signs except:

a) progressive cellular hyperplasia in the red bone marrow, with a predominance of proliferation processes

b) metaplasia of normal hematopoietic cells by leukemic cells

c) the presence of pathological foci of hematopoiesis in other cells

d) anemia with reticulocytosis and hyperbilirubinemia

13. The criterion for the diagnosis of acute leukemia is:

a) transformation of hematopoiesis due to poorly differentiated progenitor cells of classes II, III and IV

b) transformation of hematopoiesis due to maturating and mature cells

c) metaplasia of normal hematopoietic cells by leukemic ones

d) anemic, hemorrhagic septic-necrotic syndromes

14. What is the most reliable diagnostic sign of acute leukemia?

a) the presence of hemorrhagic, anemic, febrile syndromes

b) detection of Botkin-Gumprecht cells

c) detection of 30 or more blast cells in the myelogram

d) complaints of fatigue, weakness, fever, bleeding gums

15. Indicate the hematological signs of chronic lymphocytic leukemia:

a) leukocytosis ($40*10^9$/l) with a shift to the left to myelocytes

b) moderate leukocytosis, anemia with high reticulocytosis

c) leukocytosis ($60*10^9$/l), absolute lymphocytosis, detection of Gumprecht shadows

d) anemia, thrombocytopenia, leukopenia

16. How should changes in the hemogram be interpreted when a patient with sepsis has leukocytosis $40*10^9$/l with a shift in the amount to myelocytes, toxic granularity of neutrophils:

a) acute leukemia

b) leukemoid reaction of neutrophilic type

c) leukocytosis with a shift to the left

d) chronic myeloid leukemia

17. What stage of chronic myeloid leukemia is characterized by an increase in eosinophils and basophils, hyperthrombocytosis:

a) the initial stage

b) the stage of the height of the disease

c) terminal stage

18. Monocytosis > 6-7% can be in all diseases, except:

a) smallpox

b) measles

c) malaria

d) cholecystitis

e) tuberculosis

19. In which hemoblastosis tumor leukemia cells have an abnormal chromosome with a shortened long arm in the 22nd pair ("Philadelphia chromosome"):

a) acute myeloid leukemia
b) chronic myeloid leukemia
c) chronic lymphocytic leukemia
d) erythremia

20. Which hemoblastosis in the initial stage is characterized by satisfactory well-being, moderate lymphadenopathy, leukocytosis up to 10-15*10^9/l and lymphocytosis (50-70%)?

a) acute lymphocytic leukemia
b) chronic lymphocytic leukemia
c) erythremia
d) acute myeloid leukemia

APPENDIX C

Clinical cases in hematology

Clinical case 1

A 28-year-old woman consulted a local therapist with complaints of weakness, fatigue, palpitations, dizziness, headache, memory impairment, leg pain, a desire to eat dry macaroni, buckwheat, throat irritation.

It is known from the anamnesis that anemia has been detected since the age of 16. She was treated irregularly with iron preparations in courses of 2-3 weeks with a temporary effect.

Gynecological history: menstruation from the age of 14, abundant, 5-7 days after 21 days. 2 pregnancies, 2 physiological term deliveries at the age of 23 and 27.

On examination: the patient's condition is satisfactory. Height - 162 cm, body weight - 65kg. BMI – 24.08 kg/m^2. The skin and conjunctiva are pale. The nails are thin, compacted, nail edges are splitted. In the lungs, respiration is vesicular, there are no rales. Respiration rate – 18 in min. The heart tones are weakened, the rhythm is regular, during auscultation, systolic noise is heard at the top of the heart and along the left edge of the sternum, heart rate is 110 beats per minute, blood pressure is 110/70 mm Hg. The abdomen is soft, painless at palpation in all departments. The liver and spleen are not enlarged. The symptom of pounding on the lumbar region (Pasternatsky symptom) is negative. bladder and bowel habits are normal.

In the analyses: total blood count - erythrocytes $3.6*10^{12}$/l, anisocytosis, microcytosis, Hb-94 g/l, colour index - 0.6, leukocytes $5.2*10^{9}$/l, eosinophils - 1%, stab cells -3%, segmented - 57%, lymphocytes - 28%, monocytes – 9%, ESR - 25 mm/hour. Biochemical blood analysis: total protein - 77 g/l, total bilirubin - 15.3 mmol/l, indirect bilirubin - 12.1 mmol/l, serum iron - 7.6 mmol/l, ferritin - 8.8 mcg/L. ECG: sinus tachycardia, heart rate – 106 per minute, reduction of the T wave in the left thoracic V_5,V_6 leads.

1. Suggest the most likely diagnosis
2. Substantiate your diagnosis
3. Draw up and validate a plan for additional examination of the patient.

4. Which drug from the group of iron-containing drugs would you recommend to the patient? Explain your choice.

5. After 2 months of regular therapy with a drug from the iron-containing group, positive dynamics is noted: weakness and fatigue have decreased, memory has improved, palpitations do not bother, taste disorders have disappeared; in the general blood test-erythrocytes $4.2*10^{12}$/l, the average diameter of erythrocytes 7.5 microns, Hb-122g/l, colour index - 0.84, leukocytes $6,7*10^{9}$/l, eosinophils - 0%, stab cells - 2%, segmented- 59%, lymphocytes -28%, monocytes- 9%, ESR-13 mm/hour. Biochemical blood analysis: serum iron - 14.7 mmol/l, ferritin - 9.8 mcg/l. What are your further treatment tactics? Explain your choice.

Clinical case 2

Female patient Sh., 45 years old, consulted a polyclinic therapist with complaints of weakness, dizziness, hair loss, nail brittleness, dry skin.

Anamnesis: considers herself ill for 3 months, when complaints of weakness and dizziness first appeared. She didn't go to the doctor. In the following time, the symptoms began to increase, hair began to fall out, brittle nails and skin dryness appeared. Concomitant diseases: suffers from menorrhagia – menses are profuse, prolonged, for 7-10 days every 28 days.

On examination: the condition of the patient is of moderate severity. The skin and mucous membranes are pale, dry, there are no rashes. Nails with pronounced longitudinal striation, "spoon-shaped". Diffuse alopecia. There is no peripheral edema. Peripheral lymph nodes are not enlarged. Respiration in the lungs is vesicular, there are no rattling noises, respiration rate – 21 per min. The heart tones are rhythmic, the weakening of the I and II heart tones at all points of auscultation. Heart rate = 90 beats per minute. Blood pressure = 100/70 mm Hg. The abdomen is soft, painless at palpation. The liver and spleen are not palpable. The stool is formed. The kidney punch symptom is negative on both sides.

1. Suggest the most likely diagnosis

2. Substantiate your diagnosis

3. Draw up and explain a plan for additional examination of the patient.

4. After 2 days, the patient came for a repeated appointment with the results of tests: clinical blood test: hemoglobin - 95 g/l, erythrocytes - $1{,}12x10^{12}$/L. MCV 75 fl, MCH 22 pg, reticulocytes - 0.9%, platelets - $226x10^{9}$/l, leukocytes - $4{,}9x10^{9}$/l, stab cells - 4%, segmented - 51%, monocytes – $0{,}10x10^{9}$/l, lymphocytes – $1{,}7x10^{9}$/l, ESR - 36 mm/h. Serum iron 4.2 mmol/l, TIBC 82 mmol/l, transferrin saturation coefficient 23.5%, APTT 26 s, prothrombin time 14 s, fibrinogen 3.1 g/l. The gynecologist's consultation is scheduled for the next day. Prescribe treatment.

5. After 2 months of regular therapy with an iron-containing drug, the patient underwent a repeated blood test: clinical blood test: hemoglobin - 120 g/l, erythrocytes - $4{,}2x10^{12}$/ L. MCV 82 fl, MCH 28 pg, reticulocytes - 1.2%. platelets – $260x10^{9}$/l, leukocytes - $5{,}2x10^{9}$/l, stab cells - 6%, segmented - 55%, monocytes – $0{,}10x10^{9}$/l, lymphocytes – $1{,}4x10^{9}$/l, ESR - 17 mm/h. The patient is also observed by a gynecologist, takes therapy for menorrhagia, notes the normalization of menstruation. Characterize the changes in the analyses. What are your next steps?

Clinical case 3

Female patient N. 63 years old, a pensioner, attended the local doctor for an appointment, accompanied by her daughter. She complains of pronounced weakness, increasing over the last six months. Also, the daughter indicates the appearance of cognitive impairments in her mother (forgetful, sometimes lost when using household appliances).

It is known from the anamnesis that the patient suffers from arterial hypertension, the blood pressure targets were achieved against the background of combined administration of lisinopril and amlodipine. Previously, she rarely sought medical help, mainly for preventive medical examination.

The condition is satisfactory. Height 161 cm, weight 56 kg, BMI 21.6 kg/m^2. The skin and mucous membranes are pale. The lymph nodes are not enlarged. The mammary glands are soft. There is no swelling. The musculoskeletal system is within normal. Respiration is vesicular, there are no rales, respiratory rate - 16 per min. The heart tones are muffled, the rhythm is regular. Heart rate – 84 in 1 min. Blood pressure – 130/80 mmHg. The tongue is crimson, not coated.

The abdomen is soft, sensitive to palpation in the epigastric region. The liver protrudes 2 cm from under the costal arch, the edge is elastic. The spleen is not enlarged. There is no dysuria. The symptom of pounding on the lumbar region (Pasternatsky symptom) is negative. The stool is formed, regular, normal color. No sensory or motor disorders were detected.

General blood test performed urgently: erythrocytes (RBC) - 2.31×10^{12}/l, Hb – 52 g/l, MCV – 108 fl, MCH – 36.1 pg, MCHC – 391 g/l, leukocytes (WBC) - 2.8 x 10^9/l: basophils – 0%, eosinophils – 1%, stab–1%, segmented – 84%, lymphocytes - 12%, monocytes – 2%. Platelets (PLT) – 76×10^9/ L. ESR = 31 mm/hour.

1. Express and substantiate your opinion about the most likely diagnoses.

2. You are a district therapist. Suggest and substantiate further tactics of the patient's management.

3. The patient is at the appointment 1 month after. During the first two weeks she was treated in a therapeutic hospital, then continued the treatment at home. During FGS, atrophic gastritis was detected. During the past month, she received cyanocobalamin 500 mcg per day. She noted a significant decrease in weakness, but forgetfulness and difficulty in choosing words when communicating remain. Before going to the local doctor, a general blood test was performed: RBC - 3.95×1012/l, Hb – 96 g/l, MCV – 88 fl, MCH – 32.3 pg, MCHC – 348 g/L. WBC - 5.6×10^9/L. PLT – 199×10^9/ L. ESR = 25 mm/hour. What kind of treatment will you use in the future? Explain your choice.

Clinical case 4

At an appointment with a therapiutist in a polyclinic, a 61-year-old woman complains about the presence of painless tumor-like elastic formations on the side of the neck and in the axillary areas, as well as heaviness in the left hypochondrium when walking fast, increased sweating. The above complaints appeared about a year ago, gradually increased.

Objectively: the general condition is satisfactory. The skin and visible mucous membranes are of usual color. Conglomerates of enlarged submandibular, cervical, axillary, inguinal lymph nodes are palpated, elastic, painless, non-mobile, the skin above them is not

changed, symmetrically enlarged – cervical and submandibular up to 2-3 cm, axillary up to 3-4 cm, inguinal up to 4 cm in diameter. In the lungs, respiration is vesicular, no rattling noises are heard, respiratory rate is 18 per minute. The heart tones are clear, the heart rate is 78 beats per minute. Blood pressure is 120/80 mm Hg. The abdomen is soft, painless. The edge of the liver does not protrude from under the edge of the costal arch. The spleen protrudes 2 cm from under the edge of the costal arch, the edge is elastic, painless.

Total blood count: erythrocytes – 3.6×10^{12}/l, Hb – 129 g/l, platelets – 200×10^{9}/l, leukocytes - 39×10^{9}/l, stab neutrophils – 2%, segmented neutrophils – 2%, lymphocytes - 92%, monocytes - 4%, ESR – 30 mm/h, Botkin-Gumprecht shadows – 1-2 in the field of view.

1. Suggest the most likely diagnosis
2. Substantiate your diagnosis
3. Draw up and substantiate a plan for additional examination of the patient.
4. Choose and substantiate the patient's management tactics.
5. What is the prognosis for this disease, and what complications are possible?

Clinical case 5

Female patient M., 52 years old, applied to the polyclinic with complaints of unmotivated weakness, increased fatigue, a constant feeling of heaviness in the left hypochondrium, decreased appetite, early satiety. These complaints appeared about 5 months ago and gradually became more pronounced.

On examination, attention is drawn to the enlargement of the spleen (protrudes from under the edge of the costal arch by 6 cm).

Blood test: hemoglobin - 105 g/l, colour index - 0.94, leukocytes - 68.3×10^{9}/l (promyelocytes - 1%, neutrophilic myelocytes - 2%, neutrophilic metamyelocytes - 6%, neutrophilic stab - 14%, neutrophilic segmented - 58%, lymphocytes - 9%, eosinophils - 2%, basophils - 7%, monocytes - 1%), platelets - 440×10^{9}/l. The activity of neutrophil alkaline phosphatase is reduced.

1. Formulate a preliminary diagnosis.
2. Make a plan for additional examination.

3. What indicators of the blood test of this patient do not correspond to the chronic stage of the disease, substantiate the answer.

4. Cytogenetic analysis revealed the presence of a Ph chromosome, in accordance with clinical signs the patient was stratified into the intermediate risk category. Indicate the initial treatment tactics for this patient.

Clinical case 6

A 44-year-old male patient applied to the polyclinic with complaints of weakness, fatigue, shortness of breath and palpitations with little physical exertion, burning sense in the tongue, a feeling of numbness in the soles of the feet. The skin and mucous membranes are pale with a icteric tinge. The face is puffy, pale, the hair is gray. The tongue is clean, crimson, shiny, papillae are atrophied. The heart tones are muffled, weak systolic noise at the apex, on the pulmonary trunk. The liver is palpated 2 cm below the right costal arch, percussion dimensions are 15×10×8 cm. The spleen is palpated, the percussion dimensions are 13×10 cm. Reflexes are enhanced, sensitivity on the feet and hands is reduced.

Clinical blood test: hemoglobin – 63 g/l, erythrocytes – 2.6×10^{12}/l, leukocyte formula – within normal, MCV - 110 fl, Jolly bodies and Cabot's rings, poikilocytosis. Bilirubin – 55 mmol/l, indirect – 45 mmol/l. The results of sternal puncture: erythroid hyperplasia of the bone marrow, megaloblastic type of hematopoiesis, the ratio of erythroid and myeloid elements is 1:1, the number of megakaryocytes is reduced, giant metamyelocytes are determined.

1. Suggest the most likely diagnosis
2. Substantiate your diagnosis
3. Draw up and substantiate a plan for additional examination of the patient.
4. What are your further treatment tactics?
5. Name the criteria for the effectiveness of treatment of the disease.

Clinical case 7

Female patient K., 60 years old, was hospitalized in the CDH at the place of residence due to severe weakness, shortness of breath, palpitations with the slightest physical exertion. She has been feeling

weak for several years, and for the last 2 years began to notice pains in the spine. In her youth she has donated blood 8 times, has 3 children, had 4 abortions.

The district therapist, in connection with the detected anemia (erythrocytes - 3.12×10^{12}/l) prescribed Sorbifer Durules 2 tablets a day for 1.5 months. No effect was obtained.

Total blood count: erythrocytes - 1.42×10^{12}/l; hemoglobin - 50g/l, color index - 1.0; reticulocytes - 0.4%; platelets - 98×10^{9}/l; leukocytes - 2.6×10^{9}/l (stab neutrophils – 3%, segmented neutrophils - 30%, lymphocytes – 60%, monocytes – 7%), anisocytosis ++++, poikilocytosis +++; ESR - 72 mm/ hour.

1. Is it possible to establish one of the following diagnoses preliminarily: "aplastic anemia"? "acute leukemia"? "multiple myeloma"?
2. How to establish a preliminary diagnosis correctly?
3. Does the patient need to consult a hematologist, is there need for a sternal puncture?
4. Biochemical analyses revealed: total blood protein - 140g/l, albumins - 30%, globulins - 70%, an M-gradient was detected in the gamma globulin zone. Will your diagnostic search range be reduced?

APPENDIX D

Answers to hematology tests

1/ c	6/ c	11/ c	16/ b
2/ d	7/ d	12/ d	17/ a
3/ a	8/ e	13/ a	18/ d
4/ b	9/ d	14/ c	19/ b
5/ b	10/ c	15/ c	20/ b

Abbrevations

AA - Aplastic anemia
AL - acute leukemia
ALL - acute lymphoblastic leukemia
AML - acute myeloblastic leukemia
APTT - activated partial thromboplastin time
BMT - bone marrow transplantation
CLL - Chronic lymphocytic leukemia
CML - Chronic myeloid leukemia
CRF - chronic renal failure
CRP - C-reactive protein
CSF - colony-stimulating factors
CT - computed tomography
DNA - deoxyribonucleic acid
ECG - electrocardiography
ESR – erithrocite sedimentation rate
FGS - fibrogastroscopy
G-6-PDG - glucose-6-phosphate dehydrogenase
GLAP - Generalized lymphadenopathy
Hb - hemoglobin
HIV - human immunodeficiency virus
HLA - human leucocyte antigens
HSCT - hematopoietic stem cell transplantation
HTLV-1 - human T-cell virus 1
HTLV-2 - human T-cell virus 2
IDA - Iron deficiency anemia
IF - internal factor
LDH - lactate dehydrogenase
MCH - Mean corpuscular hemoglobin
MCHC - Mean cell hemoglobin concentration
MCV - Mean corpuscular volume
MM - Multiple myeloma
MRI - magnetic resonance imaging
PET - positron emission tomography with 18-fluorodeoxyglucose
PLT – platelet
POEMS - Polyneuropathy, Organomegaly, Endocrinopathy, M-protein and/or plasma cell dyscrasia, Skin changes

RBC – red blood cell
RNA - Ribonucleic acid
TIBC - total iron-binding capacity of blood serum
USA – United States of America
WBC – white blood cell
WHO – World health organization

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