

PEDIATRICS

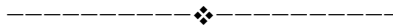
M.O. Gonchar, T.B. Ishchenko, V.A. Koval

MAIN FEATURES OF LEUKEMOID REACTIONS IN CHILDREN

Kharkiv National Medical University, Ukraine

Abstract: Leukemoid reactions are abnormal reverse reactions of blood with morphological signs similar to leukemic or sub-leukemic manifestations, but with different pathogenesis of these hematological changes. The article presents current views on etiology, pathogenesis, presentation and clinical manifestations in relation to etiological factors, diagnosis guidelines and differential diagnosis of leukemoid reactions in children, as well as therapeutic approach in these conditions.

KeyWords: leukemoid reactions, children, infections



INTRODUCTION

Leukemoid reaction (LR) is a secondary symptomatic-reversible change of the "white blood" in response to a stimulus. So it is a reactive, functional condition of hematopoietic, lymphatic and immune systems secondary to various diseases accompanied by the development of immature white blood cells in the peripheral blood, which number may exceed 50000 per 1 mm³. Thus, LR is an abnormal reaction of blood with morphological signs similar to leukemic or subleukemic manifestations, but with different pathogenesis of these hematological changes.

As reactive changes in blood are similar to hematological malignancies, it is important to differentiate them from leukemia. The causes of leukemoid reactions are usually evident with marked clinical signs (e.g., inflammation). Changes in blood are transient and blood levels return to normal when the causes disappear. There are no signs of inhibition of normal hematopoiesis.

Due to general consistent patterns and presentation of certain leukemoid reactions, their basic differences from leukemia are as follows: leukemoid reactions are mostly triggered by bacterial or viral infections, emergency stress irritants and also by various bacterial and nonbacterial pathogens, causing sensitization.

Etiology and pathogenesis

Leukemoid reactions of myeloid type develop in various infectious and noninfectious processes, septic conditions, endogenous and exogenous intoxications, severe injuries and acute hemolysis. They can particularly be observed in various infections (sepsis, tuberculosis, purulent processes, lobar pneumonia, scarlet fever, mumps, dysentery), intoxication (therapeutic intoxication, including sulfanilamide drugs, azotemia, uremia), Chlamydia, metastatic tumors of the bone marrow, ionizing radiation (radiotherapy).

Leukemoid reaction of lymphocytic and lymphomonocytic types can be observed in infectious mononucleosis, whooping cough, chicken pox, scarlet fever, rubella, tuberculosis, poisoning. Individual reactivity in children plays a great role in the development of leukemoid reactions with the exception of specific factors (viruses, helminths, toxins, infectious agents).

It should be noted that development of solid tumors is also often accompanied by neutrophilic leukemic reactions accompanied by thrombocytosis, thrombocytopenia and

• Corresponding Author:

Tatiana Ishenko, MD, PhD, Associate Professor, Department of Pediatrics 1 and Neonatology, Kharkiv National Medical University, Ukraine. E-mail: tanyatb@mail.ru

erythrocytosis.

The main link in LR pathogenesis is activation of normal hematopoiesis and excessive blood cells output to peripheral blood (reactive hyperplasia of leukopoietic tissue) and output of immature blood cells into peripheral blood.

Classification

Leukemoid reaction can be classified according to the course of the disease and the type of irritation hematopoietic lineage of the bone marrow.

According to the course of the disease LR are divided into:

- Phase of expressed manifestations
- Phase of recession
- Phase of normalization with trace reactions

According to the type of irritation hematopoietic lineage of the bone marrow LR are divided into:

1. Reactions of myeloid type
 - 1.1. Neutrophilic leukemoid reactions
 - 1.2. Eosinophilic leukemoid reactions
2. Reactions of lymphoid type
 - 2.1. Lymphomonocytic leukemoid reactions
 - 2.2. Lymphocytic leukemoid reactions
 - 2.3. Plasmocytic leukemoid reactions
 - 2.4. Leukemoid reaction with blast cells
3. Secondary (reactive) thrombocytosis
4. Secondary erythrocytosis
5. Mixed forms of leukemoid reactions
6. Rare forms of leukemoid reaction
 - 6.1. Cytopenia
 - 6.2. Leukemoid reactions of basophilic type

The main clinical manifestations of leukemoid reactions and diagnostics

Clinical presentation depends on the underlying disease that triggered leukemoid reaction.

Leukemoid reactions are basically characterized by a high level of white blood cells in peripheral blood (with the exception of cytopenic leukemoid reaction) and a distinct shift in white blood count with singular blast cells.

Leukemoid reactions of myeloid type differ from moderate leukocytosis - often to $12.0-30.0 \times 10^9/l$ and a subleukemic

shift in leukogram to myelocytes, sometimes to myeloblasts (myeloblastic type). Leukemoid disorders may be observed in blood count without significant leukocytosis, and vice versa - mild abnormalities in leukogram with stab and singular metamyelocytes in increased leukocytosis ($40.0-50.0 \times 10^9/l$). Leukemoid reaction of lymphoid type is characterized by moderate leukocytosis with absolute lymphocytosis (up to 70-90%). Other hematologic parameters usually do not undergo significant changes.

Diagnosis is based on presenting clinical signs of the underlying disease, with possible reaction and absence of symptoms of leukemic process. Absence of blasts in the peripheral blood in patients with severe leukocytosis ($30.0-50.0 \times 10^9/l$ and higher) practically excludes hemoblastosis. In diagnostic difficulty patients are referred for examination of bone marrow and lymph node aspirates.

Reactions of myeloid type are characterized by a shift to the left - from an increased number of stab cells to singular blast cells with presence of all intermediate forms. The level of hyperleukocytosis and the shift of blood count do not always correspond to the severity of the underlying disease, but depend on the response of the hematopoietic system to the infectious and toxic effects. Bone marrow aspirate most often shows an increase in immature granulocytes and irritation of myeloid lineage.

Neutrophilic leukemoid reactions develop in the following cases:

- Infections - sepsis, scarlet fever, purulent processes, diphtheria, lobar pneumonia, tuberculosis, dysentery, etc.;
- Exposure to ionizing radiation;
- Injuries of the skull;
- Intoxication (uremia, CO poisoning);
- Bone marrow metastases of malignant tumors
- Lymphogranulomatosis;
- Steroid hormones therapy.

Eosinophilic reactions ("high eosinophilia") develop in allergic processes or in diseases with allergies, as well as in parasitic diseases. They are characterized by the development of a great number of eosinophils (90%

leukocytosis at 100×10^9) and eosinophils may show excessive segmentation of nuclei.

Prognostic assessment of eosinophilic leukemic reaction is equivocal: in infections it can be considered as an evidence of immune responses, in collagen disease it can be regarded as an unfavorable sign; in parasitic and helminth diseases eosinophilia does not determine features of their course.

Lymphomonocytic leukemoid reactions develop in infectious mononucleosis (Filatov and Pfeiffer disease). It was first described in 1885 by a pediatrician N.V. Filatov. It is a disease of viral etiology. Infectious mononucleosis begins acutely with a sudden rise in temperature that persists at $39-39.5^{\circ}\text{C}$ during the day. Sometimes fever is preceded by prodromal signs: malaise, myalgia, dizziness, and systemic lymphadenopathy that subsides in 10-15 days, but slight enlargement and tenderness of lymphatic nodes may be observed for several weeks, sometimes months. Subsequently patients develop enlargement of the spleen and sore throat with necrotic changes. At the middle stage of the disease patients are found to have leukocytosis ($10.0-25.0 \times 10^9/\text{l}$). Leukogram shows 50-70% of lymphocytes with high percentage of monocytes (12 to 40-50%). Commonly there are atypical mononuclear cells, called "lymphomonocytes" (cells are larger than lymphocytes, but smaller than monocytes, with monocytic form of nucleus and intensively basophilic cytoplasm). Lymphomonocytes are modulated T- and NK-lymphocytes, which get to the bloodstream by initiation of B-lymphocytes. Mild anemia, sometimes slight thrombocytopenia and neutropenia are also observed.

Atypical mononuclear cells (reactive lymphocytes) are transformed lymphocytes, mostly reactive T-cells that provide antiviral protection and proliferative B-lymphocytes.

Atypical mononuclear cells are common not only in infectious mononucleosis. In health their number is $1/6$ of the number of lymphocytes. The number of atypical mononuclear cells can be increased in any viral infection (acute respiratory viral infections, influenza, hepatitis,

cytomegalovirus infection, herpes and pediatric infections), other infections (yersiniosis, toxoplasmosis, chlamydia), vaccination, autoimmune diseases, drug intolerance, tumors.

Lymphocytic leukemoid reactions (infectious lymphocytosis) develop in acute viral and bacterial infections and are characterized by leukocytosis with absolute lymphocytosis, an increased level of prolymphocytes in the bone marrow (in peripheral blood they are absent).

Plasmocytic leukemoid reactions occur in diseases caused by protozoa (toxoplasmosis), viral infections (chickenpox, measles, rubella), et cetera. Increased level of plasma cells (2%) in splenomegaly, blood and bone marrow is typical for this type of leukemoid reactions.

Leukemoid reactions with blast cells develop in severe viral infections (cytomegalovirus, etc.). As for blast cells, blast transformation of B-lymphocytes may be observed in the bone marrow, lymph nodes and peripheral blood.

Secondary absolute erythrocytosis is caused by increased erythropoiesis, relative hemoconcentration and polycythemia. Plasma volume is typically decreased. It is characterized by increased levels of red blood cells, hemoglobin and erythropoietin.

Thrombocytosis (platelet count more than $500 \times 10^9/\text{l}$) may be primary, as a result of tumor proliferation of megakaryocytes in chronic myeloproliferative diseases (essential thrombocythemia, idiopathic myelofibrosis, chronic myeloid leukemia), and secondary, reactive. Symptomatic (reactive) thrombocytosis is possible in malignant tumors, inflammatory diseases, following bleeding, hemolytic crises, after surgical operations and splenectomy. Secondary thrombocytosis is usually not as distinct as primary one and is rarely complicated by thrombosis (or bleeding) disappearing after elimination of the cause.

Leukemoid reactions to the tumor can be characterized by irritation of one lineage of hemopoiesis, (e.g., neutrophilia, monocytosis, eosinophilia, erythrocytosis or thrombocytosis) or with irritation of several lineages of hemopoiesis - mixed leukemoid reactions (neutrophilia and thrombocytosis, erythrocytosis and monocytosis, or other combinations). Signs of myeloma ("bone marrow in the blood") are observed in multiple metastases to the bone marrow with neutrophilia and significant left shift to myelocytes, promyelocytes and blasts. The number of leukocytes in this case varies from severe leukopenia to hyperleukocytosis. Patients are usually found to have evident anemia with reticulocytopenia and thrombocytopenia. Similar signs can be observed in acute erythroleukemia (AML-M6) and acute immune hemolysis. Diagnosis is obvious in detecting cancer cells in bone marrow aspirate or trepanobiopsy.

Leukemoid reaction with cytopenia is a rare form of myeloid reaction, when patients have a left shift in white blood count to singular immature forms secondary to leukopenia (1500-2500 leukocytes per 1 ml of blood). In such cases blood picture resembles chronic myeloid leukemia and myelofibrosis.

Leukemoid reactions of basophilic type are rare. Reactive basophilia may develop in allergic reactions, hemolytic anemia, ulcerative colitis, hypothyroidism, leukemia. Hematological diseases such as chronic myeloid leukemia, Hodgkin's disease are characterized by eosinophilic and basophilic associations.

Differential diagnosis

As reactive changes in blood are similar to leukemia, it is necessary to provide differential diagnosis (Table 1). It is generally important to consider that typical signs of tumor progression inherent to leukemia are not detected in leukemoid reactions, so metaplastic anemia and thrombocytopenia are not observed. As in leukemia, distinct immaturities of the peripheral blood to the extent of development of blast cells occur secondary to leukemoid reaction.

Table 1

The main criteria for differential diagnosis of leukemoid reactions and leukemia

| | Leukemoid reactions | Leukemia |
|-------------------------------------|---|--|
| Causes | Infectious agents, biologically active substances, products of tissue destruction | Carcinogens |
| Pathogenesis | 1. Activation of normal hematopoiesis and excess of formed elements in blood flow (reactive hyperplasia of leukopoietic tissue) 2. Exit of immature leukocytes into the bloodstream | The transformation of normal haematopoietic cells to a tumor |
| The bone marrow Peripheral blood | Focal hyperplasia of normal hematopoietic cells in proliferative reactions. The presence of blast and immature forms of leukocyte, platelet and erythrocyte hematopoiesis in the proliferative reactions. Usually leukocytosis is present. Rarely - leuko-, erythro-, thrombocytopenia is present. Signs of degeneration of formed elements | Generalized hyperplasia of tumor of hematopoietic cells Cytopenia or increased level of leukocytes is combined with the presence in the blood of leukemic blast cells. Leukemic breakdown in acute leukemia. Signs of degeneration of cells are usually absent. |
| Duration | It is temporary, reversible and it is not transformed to leukemia | It is saved during the disease |

But in most cases of leukemoid reaction, except leukemoid reaction with blasts, the number of blast elements in peripheral blood does not exceed 1-2%. It should be noted that in differential diagnosis of leukemoid reactions they usually develop on the background of severe patient's condition. Splenomegaly is not typical for leukemoid reactions and toxic granulation, vacuolization of nucleus and cytoplasm and even intravital disintegration of the nucleus may be found in neutrophil cytoplasm. Normal cellular composition of the bone marrow is indicative of leukemoid reaction.

Moreover, rapid normalization of peripheral blood occurs after elimination of the main etiological factor, which does not take place in hemoblastosis.

Therapeutic approach to leukemoid reactions in children

Prognosis of leukemoid reactions depends on the underlying disease. In most cases prognosis is favorable.

Specific therapy is generally not required. In most cases patients require treatment of the underlying disease and associated leukemic reaction.

Conflict of interests

There is no conflict of interests.

REFERENCES

1. Zhavoronok T.V. (2010). Uchastie sistemy glyutationa v podderzhanii funktsional'nogo sostoyaniya nejtrofilov pri ostrom vospalenii. Byulleten' sibirskoj medicyny, 5, 28-32.
2. Korotina O.L., Generalov I.I. (2012). Nejtrofil'nye vnekletochnye lovushki: mekhanizmy obrazovaniya, funktsii. Immunologiya, allergologiya, infektologiya, 4, 23-32.
3. Shalom G, Sion-Vardy N, Dudnik J, Ariad S. (2010). Leukemoid reaction in lung cancer patients. Israel Medical Association Journal, 12(4), 255-256.
4. Hurtado-Cordovi J, Avezbakiyev B, Frieri M, Freedman L, Gebre W. (2012). Cutaneous inflammatory malignant fibrous histiocytoma presenting with a leukemoid reaction: a case report and review of the literature. Case Reports in Medicine, 2012, 1-5. doi: 10.1155/2012/798629.
5. Hurtado-Cordovi J, Pathak P, Avezbakiyev B, Frieri M. (2012). Inflammatory malignant fibrous histiocytoma associated with leukemoid reaction or leukocytosis: a comprehensive review. International Scholarly Research Notices Oncology, 2012, 1-17. doi:10.5402/2012/946019.
6. Granger JM, Kontoyiannis DP. (2009). Etiology and outcome of extreme leukocytosis in 758 nonhematologic cancer patients: a retrospective, single-institution study. Cancer, 115(17), 3919-3923. doi: 10.1002/cncr.24480.
7. Sakka V, Tsiodras S, Giamarellos-Bourboulis EJ, Giamarellou H. (2006). An update on the etiology and diagnostic evaluation of a leukemoid reaction. European Journal of Internal Medicine, 17, 394-398.

РЕЗЮМЕ

Гончарь М.О., Ищенко Т.Б., Коваль В.А.

ОСНОВНИ ХАРАКТЕРИСТИКИ ЛЕЙКЕМОЇДНИХ РЕАКЦІЙ У ДІТЕЙ

Харківський національний медичний університет

Лейкемоїдні реакції - це патологічні зворотні реакції крові, при яких морфологічна картина має подібність до лейкемічних або сублейкемічних проявів, але патогенез цих гематологічних змін є різним. У статі представлені сучасні погляди на етіологію, патогенез, особливості перебігу та клінічні прояви в залежності від чинника виникнення, основи діагностики та диференційної діагностики лейкемоїдних реакцій у дітей, а також на лікарську тактику при цих станах.

Ключові слова: лейкемоїдні реакції, лейкоз, діти, інфекції

РЕЗЮМЕ

Гончарь М.А., Ищенко Т.Б., Коваль В.А.

ОСНОВНЫЕ ХАРАКТЕРИСТИКИ ЛЕЙКЕМОИДНЫХ РЕАКЦИЙ У ДЕТЕЙ

Харьковский национальный медицинский университет

Лейкемоидные реакции - это патологические обратные реакции крови, при которых морфологическая картина имеет сходство с лейкемическими или сублейкемическими проявлениями, но патогенез этих гематологических изменений различен. В статье представлены современные взгляды на этиологию, патогенез, особенности течения и клинические проявления в зависимости от фактора возникновения, основы диагностики и дифференциальной диагностики лейкемоидных реакций у детей, а также на врачебную тактику при этих состояниях.

Ключевые слова: лейкемоидные реакции, лейкоз, дети, инфекции

Received: 23-Feb. - 2016

Accepted: 25-Mar. - 2016