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CURRENT CONCEPTS OF MYELODYSPLASTIC SYNDROME: LITERATURE REVIEW

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Summary. Myelodysplastic syndrome (MDS) is a heterogeneous group of clonal diseases of the blood system arising from mutation of the hematopoietic stem cell and characterized by cytopenia as a result of ineffective hematopoiesis, signs of dysmyelopoiesis and a high risk of transformation into acute leukemia. More than 80% of patients with MDS are over 60 years old. About 25 thousand new cases are diagnosed annually in Europe. Given the steady aging of the European population, it is believed that the number of patients with MDS will only increase in the coming decades. In addition, signs of myelodysplasia can be detected in the bone marrow or peripheral blood, not only in MDS, but also in other non-clonal diseases. The role of thyroid hormones in hematopoiesis is known, which does not exclude the development of dysmyelopoiesis in hypothyroidism.

Key words: myelodysplastic syndrome, single-line dysplasia, severe hypothyroidism

The purpose is representation the literature data about refractory anemia

(single-line MDS) on the background of hypothyroidism.

Myelodysplastic syndrome (MDS) is a heterogeneous group of clonal diseases of the blood system arising from mutation of the hematopoietic stem cell and characterized by cytopenia as a result of ineffective hematopoiesis, signs of dysmyelopoiesis and a high risk of transformation into acute leukemia [1-3]. Dysmyelopoiesis means any quantitative and qualitative disorders that are determined in hematopoietic cells and hematopoietic tissue of the bone marrow (BM).

In Europe and the United States, the incidence in the general population is about 4-5 cases per 100 thousand population per year. More than 80% of MDS patients are older then 60 years old. Overall, approximately 25,000 new cases are diagnosed annually in Europe. Basing on the steady aging of the European population, it is believed that the number of patients with MDS will increase in the coming decades [1-6]. Therefore the study of this disease is relevant for the clinician nowadays.

The etiology, pathogenesis, classification, and differential diagnosis of MDS is unknown in 80-90% cases. Factors which increase the risk of developing MDS are: cytostatic and/or radiation therapy, smoking, contact with organic substances, insecticides, pesticides.

The study of the pathogenesis of MDS over several decades has made possible to identify few stages in the development of these diseases. The impact of damaging factors on pluripotent hematopoietic stem cells leads to the formation of clonal hematopoiesis, including all cell lines, a reactive change in the stromal microenvironment and lymphatic system, an increase of the proliferation and the apoptosis in the bone marrow. The appearance of new mutations contributes to the further clonal evolution of an existing pathological clone, which is accompanied by a decrease in apoptosis and transformation into acute leukemia [2,7,8].

The term "myelodysplastic syndrome" was proposed in 1982 by the International Working Group of Researchers from France, USA, Britain (FAB-group), which developed the classification of myelodysplastic syndrome [3,9,10].

There used to verify diagnosis of MDS according to the WHO classification

version of 2008 [11], which received significant changes in 2017. In this classification, the key term "refractory anemia" is excluded for all variants of MDS. The concept of "myelodysplastic syndrome" has become the key. There are such kinds of MDS options: MDS with linear (single-line) dysplasia; MDS with multilinear dysplasia; MDS with annular sideroblasts (MDS with annular sideroblasts and linear dysplasia, MDS with annular sideroblasts and multilinear dysplasia); MDS with an isolated deletion of the long arm of chromosome 5; MDS with excess blasts; unclassified MDS[12,13].

This clarification assumes the features of the course of the disease, the determination of the tactics of therapy and its effectiveness, the likelihood of transformation into acute leukemia. Myelodysplastic syndrome which developes after previous cytostatic or radiation exposure is classified as myeloid neoplasias.

We focused on describing of these variants of MDS due to that the refractory anemia (RA) or MDS with dysplasia are more common in therapeutic practice. The expediency of identifying them in the classification of MDS is determined by the fact that in some cases it is not possible to achieve a positive result in the treatment of anemia and at the same time, other causes of its development (tumors, systemic diseases of the connective tissue, etc.) are excluded. This RA's type are the most difficult to diagnose.

MDS with dysplasia is characterized by one or two germ cytopenia, without an increase in the percentage of blast cells in peripheral blood (<1%) and bone marrow (<5%), annular sideroblasts, and absolute monocytosis in peripheral blood. In case of a single-line dysplasia is more than 10% of cells, it is detected only in 1 hematopoietic germ. Most often, an anemia is the leading symptom in these patients. MDS with annular sideroblasts and single-line dysplasia is a variant of MDS, which is more often characterized by normo- or macrocytic anemia. The criteria of the previous variant of MDS and the detection of annular sideroblasts in the bone marrow are diagnostically significant. MDS with annular sideroblasts and multilinear dysplasia is a variant of MDS that differs from the previous one by the presence of dysplasia in the cells of erythroid, granulocytic and/or megakaryocytic germs in more

than 10%. MDS with multilinear (multiple) dysplasia has the characteristics of MDS with annular sideroblasts and multilinear dysplasia, but without detection of annular sideroblasts in the bone marrow [1,12].

The main clinical manifestations of MDS are nonspecific and are most often caused by both quantitative and qualitative changes in the hematopoietic system: cytopenic syndrome (anemic, hemorrhagic syndrome, leukopenia), infectious complications, intoxication, hepato-, splenomegaly, and autoimmune manifestations [1-5,8].

In refractory anemias (MDS with dysplasia), erythro-, leukotrocytopoiesis disorders are noted; possible lymphocytopenia, monocytosis, rarely monocytopenia. Violations of erythrocytopoiesis, usualy, are expressed by refractory normocytic, normochromic anemia, aniso- and poikilocytosis, the appearance of normoblasts in the blood, in some patients - macrocytes, ovalocytes; reticulocytopenia is often detected. In some patients, increased destruction of erythrocytes is observed, reticulocytosis is possible. In the bone marrow, the content of the elements of erythrocytopoiesis can be increased (resembling erythroleukemia), but erythrocytopoiesis is ineffective, because expressed intramedullary death of erythroid cells.

Various qualitative abnormalities are found in erythropoietic elements: a decrease in the activity of some enzymes, especially pyruvate kinase and glutathione reductase, a PAS-positive reaction in erythroblasts, changes in erythrocyte antigens, an increase of the level of fetal hemoglobin (HbF), proto- and coproporphyrins. A characteristic feature is the appearance in the blood of a pool of large unstained (peroxidase-negative) cells larger than the lymphocytes of healthy people. It is believed that these are circulating erythroblasts and/or micromegakaryocytes, which are not detected in other cytopenias [7].

The cytological and histological picture of the bone marrow allows for differential diagnosis and a differentiated approach to the choice of therapy tactics [14].

The leading symptom of MDS is cytopenia, which is diagnosed due to a

persistent decrease in hematological parameters below threshold values for more than 4 months: hemoglobin <110 g/l and/or absolute neutrophil count <1.8*10/l, and/or platelets <100 * 10/l. All diagnostic procedures are aimed at excluding reactive cytopenias or other clonal diseases of the hematopoietic system.

Prognostic factors can be divided into those that relate to the characteristics of the patient himself, and those that are determined by the characteristics of a particular variant of MDS [15].

Signs of myelodysplasia can be detected in bone marrow or peripheral blood, not only in MDS, but also in other non-clonal diseases, particularly, with B12/folate deficiency anemia, viral infections and infectious diseases, drug or other toxic load of the body, paraneoplastic reaction, autoimmune diseases; copper deficiency [16], which requires differential diagnosis.

The role of thyroid hormones in erythropoiesis is known from the literature. Thyroid hormones (thyroid gland) stimulate erythropoiesis, acting both directly and indirectly. And with normal thyroid function, there is a clear relationship between the erythrocyte index and the level of thyroid hormones [17-19].

According to WHO (2008) and some authors, with subclinical and overt hypothyroidism, the incidence of anemia is higher than in the general population, and amounts to 26.6% and 73.2%, versus 24.8%. This gives grounds to consider the presence of hypothyroidism as a risk factor for anemia [19,20].

It has been established now that a deficiency of thyroid hormones leads to a qualitative and quantitative impairment of erythropoiesis [21,23].

Development of different types of anemia is possible, including its normocytic, micro- and macrocytic variants. According to some data, the normo- and macrocytic anemia prevails in case of decrease in thyroid function, including minimal [1,2,24].

It is necessary to differentiate these disorders of hematopoiesis inside its types, as well as with anemia of chronic diseases, an iron deficiency state. Considering the multifactorial significance of thyroid hormones for hematopoiesis and its effect on the whole body [25], it is possible that several pathogenesis of anemia may be combined in one patient at the same time, which should be pay attention to the

appointment of adequate therapy. Therefore, it is of practical interest to study the features of the course of MDS against the background of decompensated hypothyroidism. We present the clinical case, which was managed by ourselves.

Conclusion.

1. The pathogenesis of the MDS is multifactorial.
2. It is necessary to make a differential diagnosis of the MDS with dysmyelopoiesis on the background of somatic pathology including thyroid diseases.

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