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Pathogenetic Measures of Nasal Discharge in Acute Leukemia

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Abstract: This article is devoted to the specific features of pathogenetic measures of nasal discharge in acute leukemia. The problems encountered in patients with acute leukemia and their solutions are studied. Cases of nosebleeds in patients with this disease were analyzed separately, and modern methods of preventing this process were studied with the help of discussions.

Keywords: acute leukemia, pathogenetic, nasal discharge, autoradiography, multipotency.

Introduction.

Significant changes in the understanding of the biology of acute leukemia in recent decades have occurred due to an increase in the analytical capabilities of laboratory diagnostics: improvement of the method of immunophenotyping, development of new sensitive molecular cytogenetic methods, including fluorescence in situ hybridization (FISH), polymerase chain reaction (PCR) with analysis of target sites genes and next generation sequencing (NGS).

Literary review and methodology.

Years of active targeted study of the pathogenesis of acute leukemia, the formation and development of diagnostic and therapeutic strategies for this disease have simultaneously become a time for combining fundamental discoveries in biology and biotechnology in general. Intensive deciphering of the mechanisms of normal hematopoiesis began several decades ago. With the help of light and electron microscopy, the maturing cells of each differentiation line were characterized quite fully. The advent of autoradiography made it possible to study their kinetic characteristics. Further advances in the study of the cellular basis of hematopoiesis are due to the development of methods for determining precursors that are unrecognizable at the morphological level, which are based on the ability of these cells to form colonies. The advent of cloning techniques, along with advances in molecular biology and genetic engineering, has completely changed modern hematology. Versatile, repeatedly confirmed studies have made it possible to obtain a fairly complete picture of the main properties of hematopoietic stem cells (HSCs). The main characteristics of HSCs were established: the ability to self-maintenance, by which it is correct to understand a very high proliferative potential, multipotency, and the ability to multilinear differentiation [1]. Decades of extensive research have been required to elucidate the last of these competencies.

HSC can produce a huge number of hematopoietic cells. Prevention of this kind "expansion" is provided by the regulation of the intensity of apoptosis, which is carried out by the Bcl2 family of proteins. These include antiapoptotic Bcl2 proteins (Bcl2, BclxL, BclW, Mcl1, A1, Boo/Diva) and proapoptotic Bcl2 proteins (Bax, Bak, Bok/Mtd). In addition, inhibitor proteins regulate apoptosis by activating the death receptors TNFR1 or DR3, which leads to the equiprobable launch of two alternative pathways, one of which ends with apoptosis, and the other prevents apoptosis induction [2, 3]. In addition, the p53 protein is referred to as apoptosis regulators. Violation of this system due to increased expression of the BCL-2 proto-oncogene that slows down apoptosis leads to an increase in the number of HSCs with stable hematopoiesis. The inability of HSCs altered by BCL-2 to be eliminated from the bone marrow "niche" underlies the competitive advantage of such cells compared to HSCs with the BCL-2 gene of the unchanged type [4]. Such mechanisms underlie the pathogenesis of leukemia. It should be emphasized that the apoptosis system plays an important role in the numerical regulation of the population of committed precursors.

An important achievement in the field of molecular biology was the study of the receptor apparatus and the molecular profile of HSCs. To date, the main series of stem cell receptors has been partially characterized. Thus, HSCs lack such line-specific antigens as CD45(R), CD2, CD4, CD8, CD38, molecules of the major histocompatibility complex. Some molecules are present only on HSCs and their early descendants: cell adhesion molecules, in particular CD34, stem cell growth factor receptor ckit, stem cell antigen Sca1, etc. [5]. At the end of the 20th century, the molecular bases of the regulation of hematogenesis (transcriptional control of hematopoiesis) began to be intensively developed. In general, hematopoiesis is a process of acquiring sequentially changing phenotypic features by blood cells as a result of the coordinated expression of specific genes. It has been established that the coordinated expression of different genes is controlled by specific transcription factors, i.e., nuclear proteins involved in the initiation or enhancement of gene expression. Transcription factors regulate the effects of a variety of differentiation and proliferative signals. Understanding the function of transcription factors is necessary to decipher the mechanisms of differentiation in the hematopoietic system. According to modern concepts, the basis of differentiation is the process of ordered gene regulation, ending with the expression of a unique set of genes. The key role of such hematopoietic transcription factors as Tal1/SCL, GATA1, GATA2, GATA3, EKLF, cMyb, AML1, HOXA1, Ikaros, E2A has been studied and established. Cell differentiation requires not only genes encoding transcription factor proteins, but also other proteins involved in signal transduction: tyrosine kinase receptors Flk1, Jak3, growth factors such as granulocytic, granulocyte-macrophage colony-stimulating (GM-CSF), thrombopoietin, erythropoietin. The functions of transcription factors are modulated by a variety of effects, including signals from cytokines, growth factors, intercellular interactions, positions in the cell cycle, etc. [1]. These mechanisms are the subject of modern research, and one can expect decisive breakthrough results in deciphering the processes of initiation of the expression of key transcription factors in hematopoietic precursors, the features of the functioning of transcription factors in the regulatory network, leading to an ordered choice of the direction of differentiation.

Of great interest is the problem of HSC plasticity. In recent years, a significant number of works have been published pointing to a new fundamental feature of HSCs — the ability to give rise to tissue cells of a certain type, to differentiate under special conditions into cells of other (unrelated) tissue types, even if they ontogenetically belong to different germ layers. This property is called plasticity, and the process of differentiation into an unusual cell type is often called transdifferentiation or, more correctly, transdetermination [6]. In recent years, a new concept has emerged, according to which all somatic stem cells have extremely wide plasticity and, in the presence of an appropriate microenvironment, are able to differentiate into any cell type. However, the origin of plasticity as such remains not fully explained. Most studies are aimed at proving/refuting the mechanism of plasticity. It is possible that it is based on the phenomenon when some genes are in a “silent” or off state (from which information is not read), while others are expressed (on state). Gene expression is probably maintained by signals from the cell microenvironment and internal mechanisms of epigenetic regulation. Thus, it can be stated that the plasticity of stem cells is currently being actively debated.

In recent decades, significant progress has been made in the formation of modern ideas about the mechanisms of malignant growth, understanding the distinctive properties of neoplastic cells, the basic mechanisms of their occurrence and the development of malignant neoplasms. Versatile and extensive studies have made it possible to establish the main properties of malignant cells: an unlimited proliferative potential of tumor stem cells, a reduced need for external signals to initiate and maintain cell proliferation, the ability to stimulate their own division by generating intracellular mitogenic signals, as well as a decrease in sensitivity to various growth inhibitory signals. In addition, it has been established that the ability of neoplastic cells to overcome replicative cell aging (immortalization), inhibit various types of programmed cell death, block specific cell differentiation, modify the microenvironment and tissues of distant organs, which ensures vascularization of tumors, plays an important role in the processes of the emergence and development of neoplasms. and recruitment of cells that promote growth, invasion, and metastasis of neoplasms makes it possible to avoid immune surveillance [7]. The development of this set of properties is based on the instability of the genome of neoplastic cells, which ensures the emergence and fixation of a large number of genetic (mutational) and epigenetic changes in a number of cell generations. Carcinogenesis is a multistage process of accumulation of mutations and other genetic changes that lead to disturbances in the regulation of cell proliferation and migration, a decrease in their sensitivity to various growth-suppressing signals, a weakening of the induction of apoptosis in them, suppression of differentiation, etc. Mutations leading to genetic instability are integral stage of tumor progression.

Modern molecular diagnostics in leukemia is based on the identification of specific gene mutations characteristic of a particular type of tumor. The main method is molecular genetic diagnostics based on PCR with analysis of target gene regions. Since the early 2010s, to decipher genes, primarily the sense sequences (sequences) of messenger RNA (mRNA) molecules, mainly classical sequencing according to P. Sanger has been used. NGS is a group of methods for determining the nucleotide sequence of DNA and RNA to obtain a formal description of its primary structure. NGS allows "read" several sections of the genome at once, which is the main difference from earlier sequencing methods. Currently, NGS has found wide application in studies of the genetic heterogeneity of acute leukemias, genes of high prognostic risk, including mutations associated with resistance to therapy, in the analysis of epigenomic disorders, as well as molecular aspects of the clonal evolution of malignant tumor clones. [9–11].

To date, a large number of gene mutations observed in acute leukemia have been established. Based on these data, a detailed molecular classification of AML and ALL has already been created [12]. In recent years, with the advent of new technological platforms and devices for NGS, the tasks of simultaneous analysis of multiple genes have become not only feasible, but are increasingly being introduced into clinical practice. Using the appropriate NGS method, it is possible to detect all known types of somatic mutations in tumor cells. This is especially important for the analysis of mutations at points in the genome, to a greater extent subject to mutational changes [13].

Thus, fundamental discoveries in the field of the biology of normal hematopoiesis, the establishment of the foundations of carcinogenesis, along with the improvement of diagnostic capabilities, made it possible to fundamentally change and form a modern view of leukemia. The evolution of ideas about the biology of acute leukemia is reflected in the classification systems. The FAB classification proposed in 2006 by a group of French, American and British hematologists served as the basis for the modern diagnosis of acute leukemia [14]. The first version of the FAB classification was published in 2006, then repeatedly revised and refined [15–17]. The classification was based on morphological, cytochemical and immunophenotypic features of leukemic cells. This made it possible to determine the lineage of the leukemic clone (myeloid, B, and Tlymphoid), to identify their subvariants, and to identify the mixed expression of myeloid and lymphoid antigens (acute leukemia with a mixed phenotype, ALSF).

The FAB classification was replaced by the 2001 WHO classification [18], which was subsequently revised in 2008 and 2017. [19]. In the modern WHO classification of tumors of hematopoietic and lymphoid tissues in 2017, the systematization of acute leukemia is based on cytogenetic and molecular genetic characteristics of leukemic cells. At the same time, the diagnostic principles

adopted in the FAB classification are preserved. A list of acute leukemia variants identified in the 2017 WHO classification, with an indication of their frequency, is presented.

True erythroid leukemia

The diagnosis of AML with an expanded erythroid germ of hematopoiesis continues to be the subject of deep research and serious discussions to date. For the first time, such a variant of acute leukemia was described by Di Guglielmo almost 100 years ago (1926) [12]. However, until now, the characteristics of this variant of leukemia remain insufficiently clear. An analysis of the results of clinical and morphological studies in the 1960s–1970s indicates that the issue of isolating erythroid leukemia has always caused difficulties. Thus, out of 32 researchers involved in the study of this problem, only 6 considered it possible to single out this leukemia as an independent variant [13]. In the FAB classification 1976–1985. Two variants of acute erythroid leukemia were characterized: erythromyelosis (Di Guglielmo's disease), in which the proliferation of cells of two lines of myelopoiesis is determined in the bone marrow - erythroid and myeloid (granulocytic or monocytic), and erythroleukemia, in which the neoplastic clone is represented only by erythroblasts [14 -16]. Accordingly, they were designated as M6a and M6v. In erythromyelosis, the blast population was characterized by morphocytochemical features characteristic of both myeloblasts (the presence of granularity, Auer rods, peroxidase and lipids) and erythroblasts (the morphological characteristics of blast cells did not have any specific features, a peculiar arrangement of the PAS positive substance in the form of globules or gaps). Numerous observations indicated that erythromyelosis is not a stable variant and sometimes turns into a myeloblastic variant.

Clinical observations indicate an unfavorable prognosis for this variant of acute leukemia associated with a specific genetic profile of blast cells and advanced age of patients [17].

Therapeutic approaches for IEP include standard chemotherapy, reduced-intensity therapy with epigenetic drugs and a selective inhibitor of the anti-apoptotic protein BCL2; they continue to be the subject of modern clinical research. A large multicenter study involving 28 European and American clinics analyzed the results of treatment of 217 patients with acute erythroleukemia. The immediate results of therapy were significantly higher with the use of intensive chemotherapy compared with hypomethylating agents. At the same time, long-term survival rates in the comparison groups were comparable. A significant improvement in prognosis was demonstrated during allogeneic hematopoietic stem cell transplantation (alloHSCT).

ACUTE LEUKEMIA OF AN UNDETERMINATED LINE OF DIFFERENTIATION

Acute leukemia of indeterminate line of differentiation was first identified as an independent category in the WHO classification of tumors of hematopoietic and lymphoid tissues in 2008. The category of acute leukemia of indeterminate line of differentiation includes acute undifferentiated leukemia, without clear signs of cellular differentiation and not classified by modern diagnostic methods, OLSF. NKCL, previously considered within the framework of acute leukemias of indeterminate line of differentiation, is defined in the 2017 WHO classification as neoplasms from lymphoid progenitors.

A characteristic feature of acute leukemias of an indeterminate line of differentiation is the absence of clear signs of differentiation along one of the hematopoietic lines. The population of tumor cells can be characterized by the absence of any lineage-specific antigens (acute undifferentiated leukemia), the presence of features of both myeloid and lymphoid affiliation (ALSF). In some cases, leukemic cells can express such a combination of markers that not only does not allow one to determine the direction of differentiation along one of the hematopoietic lines, but also classify these cases as acute undifferentiated leukemia or ALSF. In the WHO classification 2008 and 2017. these acute leukemias are subcategories of acute unclassified leukemias.

Acute leukemias with a mixed phenotype.

A characteristic feature of blast cells in patients with ALSF is the presence on tumor cells of both myeloid and lymphoid (B or T-cell) traits. The literature also presents rare observations of acute leukemias of triple (myeloid, B and T-linear) orientation of differentiation. At the same time, in

some cases, two clones of cells can be detected simultaneously, each of which expresses markers characteristic of only one line (bilinear acute leukemia). In other situations, blast cells are characterized by the expression of both myeloid and lymphoid markers (biphenotypic acute leukemias). According to the 2008 and 2017 WHO classification, OLSF is no longer recommended to be divided into bilinear and biphenotypic variants. ALSF are rarely diagnosed and account for 2–5% of all acute leukemias [109]. OLSF is more common in adults, but is also observed in childhood [110]. The first description of OLSF refers to the beginning of the 80s of the last century. In 1985, J. Mirro et al. presented a number of clinical observations of acute leukemias with simultaneous expression of myeloid and lymphoid markers by blast cells. The author designated these cases of the disease as "mixed-lineage acute leukemias". In 1987 R.P. Gale and I. Ben Bassat introduced a new term to define this group of diseases - "hybrid acute leukemia". These observations marked the beginning of the study of OLSF. For a long time, OLSF had various names: mixed lineage, bilinear, biphenotypic, hybrid acute leukemia.

Conclusion.

Fundamental discoveries in biology, improvement of diagnostic methods, deciphering the mechanisms of normal hematopoiesis, evolution of views on carcinogenesis made it possible to put forward a new concept of the hematopoiesis model and change views on leukemia. Thanks to these achievements, it became possible to revise the nomenclature of acute leukemias in the constantly improving WHO classification of tumors of the hematopoietic and lymphoid tissues, according to which new molecular genetic variants of the disease are currently being isolated.

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