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EXPERIENCE WITH HIGH-THROUGHPUT SEQUENCING, BONE MARROW TRANSPLANTATION AND TARGETED THERAPY FOR ACUTE MYELOID LEUKEMIA WITH A POOR PROGNOSIS

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ОПЫТ ПРИМЕНЕНИЯ ВЫСОКОПРОИЗВОДИТЕЛЬНОГО СЕКВЕНИРОВАНИЯ, ТРАНСПЛАНТАЦИИ КОСТНОГО МОЗГА И ТАРГЕТНОЙ ТЕРАПИИ ПРИ ОСТРОМ МИЕЛОИДНОМ ЛЕЙКОЗЕ С НЕБЛАГОПРИЯТНЫМ ПРОГНОЗОМ

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The study presents a clinical case of treating acute myeloid leukemia with an unfavorable genetic prognosis due to genotyping by high-throughput sequencing. The patient underwent related allogeneic bone marrow transplantation with targeted chemotherapy. The disease manifested itself after a new coronavirus infection. Mutations R140Q in the IDH2 gene and

P799S in the DNMT3A gene were detected by high throughput sequencing. Given the unfavorable genetic prognosis, bone marrow transplantation from an HLA-compatible sibling was performed. On day 22, COVID-19 was detected, and ruxolitinib was added to the treatment. On the 25th day, hematopoiesis was restored with the preservation of clinical and hematological remission. Ten months after transplantation, a relapse was diagnosed, for which the patient started targeted therapy with 5-azacytidine with venetoclax in combination with transfusions of donor leukocytes. The second remission was achieved after the first course. The total duration of follow-up was 24 months.

Keywords: acute myeloid leukemia, COVID-19, bone marrow transplantation, DNMT3A gene, IDH2 gene, target therapy

В исследовании приводится клинический случай лечения острого миелоидного лейкоза с неблагоприятным генетическим прогнозом, установленным в результате генотипирования методом высокопроизводительного секвенирования. Пациенту проводилась родственная аллогенная трансплантация костного мозга с таргетной химиотерапией. Заболевание манифестировало после перенесенной новой коронавирусной инфекции. Методом высокопроизводительного секвенирования определялись мутации R140Q в гене *IDH2* и P799S в гене *DNMT3A*. Учитывая неблагоприятный генетический прогноз, выполнена трансплантация костного мозга от HLA-совместимого сиблинга. На 22 сутки была выявлена новая коронавирусная инфекция, в лечение был добавлен руксолитиниб. На 25 сутки восстановлен гемопоэз с сохранением клинико-гематологической ремиссии. Через 10 месяцев после трансплантации диагностирован рецидив, по поводу которого больной начата таргетная терапия 5-азацитидином с венетоклаком в сочетании с трансфузиями донорских лейкоцитов. Вторая ремиссия достигнута после первого курса. Общая продолжительность наблюдения составила 24 месяца.

Ключевые слова: острый миелоидный лейкоз, COVID-19, морфология, мутации, цитогенетика, секвенирование

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AML – acute myeloid leukemia
CHIP – clonal hematopoiesis of indeterminate potential
COVID-19 – coronavirus disease 2019
FAB classification – Franco-American-British classification of leukemia

mRNA – messenger ribonucleic acid
PCR – polymerase chain reaction
RT-PCR – real-time polymerase chain reaction

Acute myeloid leukemia (AML) is characterized by uncontrolled proliferation with impaired differentiation of hematopoietic progenitor cells. In this case, aberrant activation of signal pathways due to mutations in various genes is a central link in the pathogenesis of AML [1]. Current research had established a dynamic process of clonal evolution that started long before the diagnosis of AML was established and is constantly changing depending on selective pressure, including chemotherapy [2].

The purpose of the study is to analyze the case of diagnosis and treatment of acute myeloid leukemia with an unfavorable genetic prognosis established as a result of genotyping by high-throughput sequencing in a mature patient.

Clinical observation. Bone marrow and peripheral blood samples of patient K., 59 years of age, were studied and treated using related allogenic bone marrow transplantation. The total duration of the patient's observation was 24 months.

Diagnostics of AML were based on the clinical features, cytological analysis of blood and bone marrow, cytochemical research and immunophenoplasty [2, 3].

Cytogenetic research, real-time polymerase chain reaction (PCR) for specific genetic anomalies and detection of gene mutations in 141 genes by high-throughput sequencing on MiSeqDX (Illumina, USA) was performed using the QIAseq Targeted DNA Human Myeloid Neoplasms Panel (Qiagen, USA)

In the case study, the disease manifested while treating a patient from COVID-19 with bilateral pneumonia in an infectious disease hospital. The clinical features of this disease were subfebrile temperature up to 38 °C and dry cough, which persisted after receiving a negative smear for SARS-CoV-2.

In the clinical analysis of the blood, the level of hemoglobin was 108 g/l, leukocytes – $2.0 \times 10^3/\mu\text{l}$ (blasts – 41 %), and platelets – $173 \times 10^3/\mu\text{l}$. In the bone marrow at cellularity of 28,000/ μl , blast cells accounted for 42 %. Cytochemical reactions to lipids were positive in 68 % of blasts, and diffuse glycogen was detected in the cytoplasm of 14 % of blast cells. Immunophenotypically, leukemic cells in 23.5 % were characterized by the expression of CD11a, CD13, CD15, CD22, CD33, CD34, CD45, CD117, CD123, HLA-DR, MPO. Based on morphological data, was diagnosed AML, M2 according to the FAB classification [5].

A cytogenetic study identified an aberrant karyotype of leukemic blasts with aneuploid and normal subclones: 48, XX, +11, +mar / 46, XX [5]. mRNA transcripts of chimeric genes BCR-ABL, CBFB-MYH11, MLL-MLLT3, MLL-MLLT4, MLL-MLLT10, RUNX1-RUNX1T1, as well as mutations D816 in the c-KIT gene, D835 in the FLT3 gene, internal tandem duplications of FLT3 and insertions in the exon 12 NPM1 genes were not detected by RT-PCR.

Next-generation sequencing was used to determine pathogenic mutations in the DNMT3A and IDH2 genes, in

which the amino acid substitutions P799S and R140Q in the proteins they encode (allelic load 40.0 % and 43.0 %, respectively) were detected. In addition, in the coding sequences of the CBL, JAK3 and GATA1 genes, mutations were identified that cause amino acid substitutions P823T, T8M and G229S (allelic load 11.0 %, 53.0 % and 36.0 %, respectively), but whose clinical significance in AML is not established [2, 3]. The coding sequences of the other studied genes corresponded to the reference ones in GeneBank. A feature of the case was also an increased expression level of the mRNA of the WT1 gene (13833×104), detected by PCR.

The patient was treated according to the scheme, including two courses of induction-consolidation remission «7+3ida»: cytarabine 100 mg/m² from the 1st to the 7th day, idarubicin 12 mg/m² from the 1st to the 3rd days [2]. In the postcytostatic period, stomatitis, and neutropenic fever, for which the patient received broad-spectrum antibiotics and antifungal drugs, were observed. On the +25th day after the end of the first course of induction, count of the blasts in the bone marrow aspirate was 3 %, the first remission was detected. After the second course, «7 + 3ida» remission was persisted.

Due to the unfavorable prognosis and the presence of a related HLA-identical sibling (brother, 62 years old), allogeneic bone marrow transplantation was performed. To prepare for transplantation, the conditioning regimen «treo+flu» was used: treosulfan 15.0 from –5 to –3 days in combination with fludarabine 50 mg from –6 to –2 days. To prevent acute graft-versus-host disease, cyclophosphamide was used on days +3 and +4, followed by mycophenolate mofetil and tacrolimus. On day 22, the patient was diagnosed with COVID-19, and therefore ruxolitinib was added to the treatment with a positive effect. Hematopoiesis was restored on the 28th day, hematological remission and 100 % donor chimerism were maintained at control analyses.

Six months after the transplantation, the patient developed a hypofunction transplant with a remaining 100 % donor chimerism, and transfusions of donor leukocytes were performed twice. However, ten months after transplantation, the patient showed deeper leukopenia (leukocyte – $1.0 \times 10^3/\mu\text{l}$), anemia (hemoglobin 80 g/l), thrombocytopenia (platelets – $16.0 \times 10^3/\mu\text{l}$). In the bone marrow aspirate – blast infiltration of 19.6 % with cellularity of 11000/ μl . Immunophenotyping revealed a pool of blast cells expressing CD11a, CD22, CD34, CD45, CD117, CD123, HLA-DR, and MPO. The level of donor chimerism for STR loci was 76 %. The first recurrence of AML was detected.

In the case described, an aberrant karyotype 48, XX, +11, +mar/46, XX [5] was determined at the onset of the disease, and pathogenic mutations in the DNMT3A and IDH2 genes were detected by high-throughput sequen-

cing. It is known that some mutations associated with myeloid neoplasms are detected in peripheral blood leukocytes of healthy people over the age of 60 in about 10 % of cases, which is defined as clonal hematopoiesis of indeterminate potential (CHIP). The most common mutations in CHIP are nucleotide substitutions in the DNMT3A and TET2 genes encoding epigenetic regulators. The hypomethylating agent 5-azacytidine inhibits deoxynucleotide methyltransferases and causes global hypomethylation. This therapy is actively used in myeloid tumors and is more effective than standard chemotherapy in elderly and senile patients [3, 4].

Changes in DNA methylation also occur in patients with mutations in the genes encoding isocitrate dehydrogenase (IDH) enzymes. They change the functional activity of the enzyme that converts isocitrate to R-2-hydroxyglutarate instead of α -ketoglutarate. R-2-hydroxyglutarate acts as an oncometabolite and diffuses into the nucleus, where it promotes neoplasia by inhibiting α -ketoglutarate-dependent dioxygenases. IDH2 mutations also lead to increased sensitivity to proapoptotic BH3 mimetics, such as the small molecule BCL-2 inhibitor venetoclax, probably due to altered mitochondrial function associated with an increase in R-2-hydroxyglutarate [6].

Following the genetic profile, the targeted therapy scheme of 5-azacytidine 100 mg on days 1–5 in combination with venetoclax 400 mg was started. After the first course of target therapy, the second remission of AML was achieved. Subsequently, due to the continued hypofunction of the bone marrow graft, three consolidating courses of 5-azacytidine with venetoclax were performed in combination with transfusions of donor leukocytes. The total duration of observation of the patient was 24 months, the duration of the first remission – 13 months, and the second remission – 7 months.

In this case study, in an adult patient with two pathogenic mutations in the DNMT3A and IDH2 genes and an aneuploid karyotype, the first long-term remission of AML was achieved after the use of standard chemotherapy and allogeneic bone marrow transplantation. However, ten months after transplantation, a recurrence was developed. The second remission of AML was achieved through the application of targeted therapy with 5-azacytidine and venetoclax following the genetic profile of AML.

Conclusions. Cooperation of mutations in the genes DNMT3A, IDH2 and aberrant aneuploid karyotype in acute myeloblastic leukemia oncogenesis have been identified in the adult patient. These data may hold the promise of personalized medicine, leading to routinely available high-throughput sequencing tests. Including bone marrow transplantation and target therapy makes it possible to achieve long-term first and second remissions, despite the unfavorable prognosis of AML.

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AXIOMS AND THEOREMS IN THE TREATMENT OF LARGE AND GIANT POSTOPERATIVE HERNIAS

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АКСИОМЫ И ТЕОРЕМЫ В ЛЕЧЕНИИ БОЛЬШИХ И ГИГАНТСКИХ ПОСЛЕОПЕРАЦИОННЫХ ВЕНТРАЛЬНЫХ ГРЫЖ

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This work presents the treatment of patients with large and giant incisional ventral hernias. The results of surgical treatment do not allow surgeons to stop searching for and eliminating/reducing all risk factors which cause an unfavorable outcome of anterior abdominal wall surgery, both in the near and long-term postoperative period. The article discusses: terminology, classification, pathoanatomic changes in the compromised anterior abdominal wall, features of surgical procedures, complications, and their prevention and risks of hernia recurrence. The anatomical and physiological features of the anterior abdominal wall and muscle frame, morphologically altered in the hernia gate area as a result of previous surgical interventions, as well as the constitutional features of patients, are a problematic point of hernioplasty.

Keywords: *large and giant postoperative ventral hernias, surgical treatment, complications, recurrence*

Представлено лечение пациентов с большими и гигантскими послеоперационными вентральными грыжами. Результаты оперативного лечения не позволяют хирургам остановиться в поиске и ликвидации/снижении всех факторов риска, обуславливающих неблагоприятный исход хирургии передней брюшной стенки, как в ближайшем, так и в отдаленном послеоперационном периоде. Рассмотрены: терминология, классификация, патологоанатомические изменения в компрометированной передней брюшной стенке, особенности способов оперативных вмешательств, осложнения и их профилактика, риски рецидива грыж. Особенно сложным моментом герниопластики являются анатомо-физиологические особенности передней брюшной стенки и мышечного каркаса, морфологически измененные в зоне грыжевых ворот в результате предыдущих хирургических вмешательств, а также конституционных особенностей пациентов.

Ключевые слова: *большие и гигантские послеоперационные вентральные грыжи, оперативное лечение, осложнения, рецидивы*