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WISKOTT–ALDRITCH SYNDROME (A CASE FROM PRACTICE): ALLOGENEIC BONE MARROW TRANSPLANTATION

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ABSTRACT. The article presents the results of our own clinical observation of a case of Wiskott-Aldrich syndrome, a combined primary immunodeficiency characterized by an X-linked recessive type of inheritance and manifested in a third of patients by a triad: recurrent microbial-inflammatory diseases, eczema (atopic dermatitis) and bleeding due to thrombocytopenia and platelet dysfunction. The disease occurs only in males and accounts for approximately 3% of all primary immunodeficiencies. In the given clinical example, the patient's diagnosis is based on a typical clinical picture (eczema, thrombocytopenia, immunodeficiency) and confirmed by the method of molecular genetic diagnostics. In the presented clinical example, it is relevant to describe the stages of therapy for a patient who, despite the high risk of life-threatening complications, ended with an unrelated allogeneic hematopoietic stem cell transplant from a fully compatible unrelated donor. During the follow-up of the child, it was found that, despite all the possible risks of complications, satisfactory functioning of the transplant was achieved with the restoration of platelet hematopoiesis. The post-transplant period, complications, therapy, and recommendations are described. The study of the presented clinical example will help to increase the effectiveness of early diagnosis of Wiskott–Aldrich syndrome and timely develop the correct treatment plan for the patient.

KEYWORDS: *child, Wiskott–Aldrich syndrome, thrombocytopenia, allogeneic unrelated bone marrow transplantation, complications, therapy, recommendations*

СИНДРОМ ВИСКОТТА–ОЛДРИЧА (СЛУЧАЙ ИЗ ПРАКТИКИ): АЛЛОГЕННАЯ ТРАНСПЛАНТАЦИЯ КОСТНОГО МОЗГА

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РЕЗЮМЕ. В статье представлены результаты собственного клинического наблюдения случая синдрома Вискотта–Олдрича — комбинированного первичного иммунодефицита, который характеризуется Х-сцепленным рецессивным типом наследования, и у трети больных проявляется триадой: рецидивирующими микробно-воспалительными заболеваниями, экземой (атопическим дерматитом) и кровотечениями, обусловленными тромбоцитопенией и дисфункцией тромбоцитов. Заболевание встречается только у лиц мужского пола и составляет приблизительно 3% всех первичных иммунодефицитов. В приведенном клиническом примере диагноз пациенту установлен на основании типичной клинической картины (экзема, тромбоцитопения, иммунодефицит) и подтвержден методом молекулярно-генетической диагностики. В представленном клиническом примере актуальным является описание этапности проведения терапии пациенту, которая, несмотря на высокий риск развития жизнеугрожающих осложнений, завершилась проведением неродственной аллогенной трансплантации гемопоэтических стволовых клеток от полностью совместимого неродственного донора. В ходе последующего наблюдения за ребенком было установлено, что, несмотря на все возможные риски развития осложнений, было достигнуто удовлетворительное функционирование трансплантата с восстановлением кроветворения по тромбоцитарному ростку. Описаны посттрансплантационный период, осложнения, проведенная терапия и рекомендации. Изучение представленного клинического примера поможет повысить эффективность ранней диагностики синдрома Вискотта–Олдрича и своевременно выстроить правильный план лечения пациента.

КЛЮЧЕВЫЕ СЛОВА: *ребенок, синдром Вискотта–Олдрича, тромбоцитопения, аллогенная неродственная трансплантация костного мозга, осложнения, терапия, рекомендации*

Wiskott–Aldrich syndrome (WAS) is a combined primary immunodeficiency characterized by X-linked recessive inheritance. In one third of patients manifests with the triad of recurrent microbial inflammatory diseases, eczema (atopic dermatitis) and bleeding due to thrombocytopenia and platelet dysfunction [1, 2]. The disease occurs only in male individuals. Female individuals do not suffer from this pathology, but can transmit the defective gene to the next generation. The gene responsible for the development of the disease (WAS-gene) is located on the short arm of the X chromosome Chr.11.22 and consists of 12 exons encoding 502 amino acids [3].

According to the literature, the incidence of boys born with WAS is 1 in 250,000 live births without ethnic or geographic predominance, which is approximately 3% of all primary immunodeficiencies [3, 4].

In WAS, WAS-protein (WASP) synthesis is reduced or not produced at all. The functions of this protein have not been fully understood to date. However, it has been found to play a key role in actin protein polymerization and cytoskeleton formation. WASP is expressed only in nucleus-containing cells of the hematopoietic system and is of exceptional importance for signal transduction from cell surface receptors to the actin cytoskeleton, which is dynamically regulated by it. Defects in the formation of all cellular structures, the formation of which depends on the cytoskeletal reorganization of actin filaments, are observed when WASP synthesis is reduced. This results in impaired function of cells that normally express WASP (leukocytes and platelets). It has been found that the concentration of myosin, which also takes part in the formation of the cytoskeleton, is significantly reduced in platelets of patients with WAS [5].

The full function of actin cytoskeleton plays an important role at the stage of platelet production by megakaryocytes in bone marrow (BM), as well as for the realization of their adhesive, aggregation and other functions. Thrombocytopenia and decreased platelet size is a consistent laboratory sign of WAS. Usually the platelet count varies from 30 to 140 G/L, but periodically decreases to 10–30 G/L. In the BM punctate of patients, the absence of megakaryocytes is determined. The clinical picture of the disease is characterized by the development of hemorrhagic syndrome, which intensifies against the background of infectious process, chronic posthemorrhagic anemia and enlargement of the spleen [5, 6].

B- and T-lymphocyte synthesis, formation of immune synapses of T-lymphocytes, chemotaxis of WASP-deficient leukocytes, cytolytic activity of NK cells, IgG-mediated phagocytosis and, consequently, antigen presentation are impaired in patients with WAS. These changes lead to the development of recurrent bacterial, fungal and viral infections [3, 6].

In the first year of life, the presence of WAS in a child can be suggested by a characteristic triad of clinical symptoms: bleeding, eczema, and recurrent infections [1, 7]. The disease usually debuts with bloody diarrhea, petechial rash on the skin, oral mucous membranes, prolonged healing of the umbilical wound, and eczema. The classical triad usually develops in only one third of children with WAS, and in the remaining cases, the manifestations may be in the form of thrombocytopenia or infectious diseases, or isolated eczema [8]. There is an increased incidence of autoimmune diseases such as hemolytic anemia, vasculitis, glomerulonephritis, and inflammatory bowel disease in patients with WAS [9].

The only curative method of treating WAS is hematopoietic stem cell transplantation (HSCT) from an HLA-compatible related or unrelated donor. The best results of transplantation are noted in patients in the first two years of life in the absence of severe infectious and/or autoimmune complications [1, 2, 6]. Introduction of hematopoietic stem cells (HSC) from a donor to a recipient is performed for partial or complete replacement of hematopoiesis after cytostatic and/or radiation therapy [8, 10].

Depending on the donor, HSC are divided into autologous (auto-HSCT) — the recipient is the donor of HSC, and allogeneic (allo-HSCT) — HSC are obtained from related and unrelated donors. The main sources of HSC for transplantation are BM cells (HSC content 1–3%) and peripheral blood stem cells (PBSC) — HSC content in norm is 0,01–0,1%, after mobilization it is up to 2%. Less often the source of HSC is umbilical cord blood — the content of HSC at the 38th week of pregnancy is about 1%. The qualitative composition of the transplant depends on the source of its obtaining. Each source has its advantages and disadvantages, which are considered in the context of the nature of the disease, HLA-system gene compatibility, age, weight of the recipient and donor when choosing a transplant [10–12].

It should be noted that selection of an unrelated donor with optimal characteristics is impossible for 30%

of patients due to allelic polymorphism of HLA genes. Reduced degree of HLA-compatibility creates additional risks of severe complications, namely, it increases the probability of graft-versus-host reaction (GVHR) [10]. When making a decision on HSCT, it is necessary to analyze the correlation between the risk of death, development of severe complications associated with the disease, and the risk of HSCT procedure [12–14].

The success of therapy also depends on such significant factors as conditioning regimen, GVHR prophylaxis, concomitant therapy, the status of the underlying disease and clinical features of its course [11, 15, 16].

Aim. To study clinical manifestations of WAS and methods of its treatment on the example of a particular patient.

We present **a clinical case of our own observation** of a patient with WAS.

The boy K., 5 months old, was in the pediatric department of the City Children's Clinical Hospital No. 1 in Donetsk.

He was admitted with his parents' complaints about changes in clinical blood analysis in the form of moderate anemia and thrombocytopenia.

Anamnesis. The child was born from VIII pregnancy at 39 weeks gestation. The pregnancy proceeded against the background of edema of pregnancy, chronic cytomegalovirus infection (CMVI), genetic thrombophilia. I pregnancy ended in childbirth — the boy died at the age of 3 months, according to the mother's words, the child was diagnosed with leukemia (a child from the first marriage). II, III, IV pregnancies ended with medical abortions. V pregnancy ended in childbirth — the boy died at the age of 7 months (child from the second marriage). VI pregnancy ended in childbirth — the girl is healthy (child from the third marriage). VII pregnancy ended in childbirth — boy died at the age of 3 months, the child was diagnosed with congenital CMVI, pneumocystis pneumonia (child from the fourth marriage). These labor was V, term, normal; Apgar score was 7/8 points. The baby's weight at birth was 4300 g.

By three months of life, the child had twice suffered intestinal infection caused by *Klebsiella pneumoniae*. Examination in the department revealed thrombocytopenia — 50 G/L, anemia of average severity. Due to the revealed changes in blood tests he was hospitalized in the oncohematology department of the State Institution "Institute of Emergency and Reconstructive Surgery named after V.K. Gusak". with the diagnosis: acute CMVI, active phase, primary immunodeficiency, severe anemia, thrombocytopenia.

A positive titer of IgM and IgG to cytomegalovirus was detected, a BM puncture was performed. Myelogram showed the following changes: BM punctate is small cellular, there are no BM elements (megakaryocytic and erythrocytic sprout). It is possible overdilution with peripheral blood. It was recommended to repeat the BM puncture to clarify the diagnosis. Normal human immunoglobulin was administered to the child in the department. The child was consulted by an infectious disease specialist and diagnosed with congenital CMVI, manifest generalized form (hematological, hepatic) against the background of congenital immunodeficiency. Then the child was transferred to the intensive care unit of City Children's Clinical Hospital No. 1 in Donetsk for treatment of CMVI. In the ward he received human anti-cytomegalovirus immunoglobulin.

Due to the severity of the anemic syndrome, thrombocytopenia, neutropenia, lack of positive dynamics from the therapy, the child was repeatedly transferred to the oncohematology department of the "Institute of Emergency and Reconstructive Surgery named after V.K. Gusak". A repeated BM puncture was performed: BM preparations were cellular, erythroid sprout was of normoblast type. Blood system diseases were excluded. The child underwent transfusion of thromboconcentrate, infusion of human anti-cytomegalovirus immunoglobulin. For further treatment and observation, the child was transferred to the pediatric department of City Children's Clinical Hospital No. 1 in Donetsk.

At the time of our examination, the general condition of the child was severe. Body temperature was 36.7 °C, heart rate was 111 per minute, respiratory rate was 26 per minute. The weight of the child was 9580 g. Consciousness was preserved, active. Skin was pale. There were traces of intravenous injections on the skin of temples, elbow bends, wrist joints. On the skin of the face, trunk there were elements of papular rash, areas of desquamation, single elements of petechial rash on the trunk. Visible mucous membranes were pale pink, normally moist. Above the lungs percussion there was clear pulmonary sound.During the auscultation we heard puerile respiration. Heart tones were muffled, rhythmic. The abdomen was not enlarged in volume, accessible to palpation. The liver protrudes 2 cm from under the edge of the rib arch, the spleen was 2.5 cm

below the edge of the rib arch. Stool was 1–2 times a day, mushy. Urination was not disturbed.

The child was examined.

Anemia of varying severity, neutropenia and thrombocytopenia (23–95 g/L) were registered in the clinical blood analysis throughout the observation.

Blood biochemical analysis parameters were within the age normal range.

The determination of CD4 lymphocyte subpopulation was carried out — 1628 cells (42,9%), which corresponds to the age norm.

Ultrasound examination of abdominal cavity organs was without pathology.

Neurosonogram — there was slight ventriculodilation, lenticulostriary vasculopathy.

Echocardiography (EchoCG) — there was minimal tricuspidal and pulmonal regurgitation, aberrant chorda in the left ventricular cavity.

On X-ray examination of chest organs there was no pathology.

The patient was consulted by otorhinolaryngologist, ophthalmologist, neurologist, allergologist, immunologist — recommendations for further examination and treatment were given.

Geneticist consultation: the child was diagnosed with WAS. For technical reasons, specific molecular genetic diagnosis of this syndrome could not be realized. Medical and genetic counseling of the family was carried out.

In the course of telemedicine consultation with the staff of the Dmitry Rogachev National Medical Research Center for Pediatric Hematology, Oncology and Immunology of the Russian Ministry of Health a conclusion was obtained. According to the submitted documents, taking into account the aggravated family history (death of male children in infancy), clinical symptoms, and laboratory changes, the child is likely to be diagnosed with primary immunodeficiency syndrome. Molecular genetic examination "Immunologic Panel" and TREC/KREC determination were recommended. Blood was collected for this study, the blood sample was sent to the immunology department of the Dmitry Rogachev National Medical Research Center for Pediatric Hematology, Oncology and Immunology of the Russian Ministry of Health. After receiving the results of genetic studies, a telemedicine consultation with the staff of this institution was repeated. The following conclusion was received: according to the data of the genetic examination, the patient was confirmed to have primary immunodeficiency: WAS. The only curative method of treatment is HSCT from an unrelated or haploidentical donor.

A telemedicine consultation with the staff of the Russian Children's Clinical Hospital of the Federal State Budgetary Educational Institution of Higher Education "N.I. Pirogov Russian National Research Medical University" of the Ministry of Health of Russia was conducted. Final diagnosis based on the results of the consultation: primary immunodeficiency. WAS. Congenital CMVI. Anemia of mild severity. Dysplastic cardiopathy. It was recommended to continue the prescribed therapy, to conduct HLA-typing of the child, parents, to start searching for a compatible BM donor with subsequent BM transplantation (HSC). To correct thrombocytopenia it is reasonable to prescribe romiplostim or eltrombopag. Platelet transfusion is indicated only in case of bleeding.

In the department, the child received valganciclovir, co-trimoxazole, fluconazole, colecalciferol, thromboconcentrate transfusions, normal human immunoglobulin, and iron preparations.

Repeated telemedicine consultation was carried out at the Russian Children's Clinical Hospital of the Federal State Budgetary Educational Institution of Higher Education "N.I. Pirogov Russian National Research Medical University" of the Ministry of Health of Russia. The diagnosis remained the same. Conclusion: haploidentical BM transplantation in a patient with this diagnosis carries a very high risk of life-threatening complications, which makes its feasibility doubtful. The search for an unrelated compatible BM donor was recommended, and the current treatment (romiplostim, normal human immunoglobulin, valganciclovir, co-trimoxazole) was continued.

The child was started on romiplostim therapy — 8 injections.

At the age of 1 year 6 months, the patient was admitted to the Clinic of the R.M. Gorbacheva Research Institute of Pediatric Oncology, Hematology and Transplantology in satisfactory condition for examination and decision on allogeneic BM transplantation. At the time of admission the hemogram were anemia of medium severity, thrombocytopenia of IV degree. Due to severe thrombocytopenia the patient was on romiplostim therapy, which was suspended due to the lack of the drug. Infectious complications were represented by congenital CMVI, generalized form. He received therapy with vanganciclovir. Taking into account the nature and course of the disease, the patient

was shown to perform allo-HSCT. A search for a donor in the Russian registry was activated.

A fully compatible unrelated donor was found. The child was hospitalized for allo-HSCT. The conditioning regimen of nonmyeloablative FluTreoThio was tolerated relatively satisfactorily. Unrelated allo-HSCT from a fully compatible donor was performed. The graft source was BM. GVHR prophylaxis, drug administration was tolerated without immediate complications.

The early post-transplantation period was complicated by the course of gastrointestinal tract mucositis of II-III degree. From day 6 he received partial parenteral nutrition. The first wave of febrile neutropenia — from day 9 with response to empirical antibacterial therapy, apyrexia was achieved by day 11.

Infectious complications — pulmonary aspergillosis. Against the background of etiotropic therapy, positive dynamics was achieved in the form of regression of previously existing foci according to computed tomography.

Recovery of donor hematopoiesis by the platelet sprout (more than 20 thousand/μL) was recorded by day 14. Platelets more than 50 thousand/μL were recovered by the 16th day and more than 100 thousand/μL by the 21st day. The recovery of hematopoiesis in the leukocytic sprout was registered on the 22nd day, in neutrophils it was registered on the 23rd day.

The graft engrafted independently without stimulation with granulocyte colony-stimulating factor on the 25th day, chimerism was complete donor.

Therapy of acute grade I GVHR (grade II skin) produced a complete response to systemic glucocorticosteroid therapy from day 25.

The graft functions satisfactorily, chimerism is full donor, hematransfusion-independent. Basal immunostimulating therapy was performed: tacrolimus, mycophenolate mofetil.

The patient was diagnosed with the following clinical diagnosis.

Primary diagnosis. Primary immunodeficiency. WAS (mutation in WAS gene in homozygous state). Allogeneic unrelated BM transplantation.

Complication. Bilateral multisegmental pneumonia of mixed etiology (CMVI, *Actinomyces* spp., *Streptococcus salivaris*). Probable invasive pulmonary aspergillosis. Postcytostatic pancytopenia (severe anemia, grade IV thrombocytopenia, grade IV neutropenia). GI mucositis of II–III degree. Febrile neutropenia. Acute GVHR grade I (skin grade II), complete response. Colonization of the GI tract with *Klebsiella pneumoniae*, *Esherichia coli*, *Candida lusitaniae*. Colonization of the pharynx with *Str. viridans group*, *Str. epidermidis*. Urinary tract infection, asymptomatic bacteriuria (*Str. epidermidis*, *Enterocccus faecalis*). Reactivation of CMVI, chronic course.

Secondary diagnosis. Presence of other transplanted organs and tissues.

Therapy given: platelet concentrate, normal human immunoglobulin; chemotherapy: fludarabine, treosulfan, thiotepa; immunosuppressive therapy: tacrolimus, mycophenolate mofetil, methylprednisolone; concomitant therapy: Omeprazole, ciprofloxacin, acyclovir, voriconazole, co-trimoxazole, pancreatin in microgranules, cefoperazone with sulbactam, ganciclovir, allopurinol, fluconazole, paracetomol.

The patient was given recommendations:

- observation of pediatrician, hematologist, immunologist;
- continue taking tacrolimus, mycophenolate mofetil, folic acid, valganciclovir, variconazole, cotrimoxazole, pancreatin, omeprazole; if the IgG level decreases less than 4.0 g/l, it is recommended to carry out replacement transfusion with normal human immunoglobulin;
- control of analyzes: clinical blood analysis, biochemical blood analysis, urinalysis, quantitative polymerase chain reaction to cytomegalovirus, Epstein-Barr virus, herpes virus, determination of IgG level;
- physical therapy, rehabilitation, high-calorie, high-protein, hypoallergenic diet;
- immunomodulators and intramuscular injections are contraindicated;
- medical withdrawal from vaccination;
- repeated hospitalization at the R.M. Gorbacheva Research Institute to control the therapy.

Conclusion. Thus, the peculiarity of this case is the presence in the patient of the classical triad of symptoms characteristic of WAS (eczema, thrombocytopenia, immunodeficiency), with confirmation of the diagnosis by molecular genetic study. It is indicated that during the treatment of the child, combined therapy of infectious manifestations of this primary immunodeficiency, eczema, substitution therapy with intravenous immunoglobulin and thrombocytopenia allowed to achieve only a temporary positive effect. In the

presented clinical example it is relevant to describe the stages of therapy of the patient, which, despite the high risk of life-threatening complications development, ended with allo-HSCT from a fully compatible unrelated donor. During the follow-up of the child it was found that despite all possible risks of complications development, satisfactory functioning of the transplant with restoration of hematopoiesis by the platelet sprout was achieved. The study of the presented clinical case will help to improve the efficiency of early diagnosis of WAS and timely build a proper treatment plan for the patient.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

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ЛИТЕРАТУРА

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