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Bone Marrow Transplantation as a Method of Choice in Treatment of Gain-of-Function Mutations in STAT1. Case Report

Трансплантация костного мозга как метод выбора при лечении мутации с усилением функции (Gain-of-Function Mutation) в STAT1. Клинический случай

Abstract

Gain-of-function mutations in signal transducer and activator of transcription 1 (STAT1) was described. This disease is often accompanied by severe immunodeficiency. In the treatment of such patients, antifungal, antibacterial therapy is used, which is not always effective. Some patients underwent bone marrow transplantation with various efficacy. The indications for bone marrow transplantation in this pathology remain uncertain. This causes difficulties for doctors and patients in making the choice of bone marrow transplantation. In this paper, we present a case of successful peripheral blood stem cell transplantation in a patient with gain-of-function mutations in STAT1. A boy at the age of 1 year and 8 months with gain-of-function mutations in STAT1 had a recurrent course of candidial infection (esophagitis, stomatitis), repeated lung lesions, repeated pneumonia with a poor or short-term response to antifungal and antibacterial drugs. Recurrent infections led to delay in physical development. Cellular immunodeficiency (decrease of CD4+ T-lymphocytes) was identified. The inexorable course of the infectious syndrome, deterioration of the quality of life of the patient and his family led to the decision to undergo bone marrow transplantation on demand of the child's parents. The possible favorable prognostic factors for successful bone marrow transplantation were early age, presence of gain-of-function mutations in the STAT1 mutation variant, and a related donor. The patient has survived. However, there were complications during the transplantation in the form of acute and then chronic graft-versus-host disease (GvHD). There was the reconstitution of immunity, the infectious process did not manifest. The patient has become active; at this time, he does not differ in his physical development from his peers. The decision to carry out transplantation should be made individually, based on the severity of immunodeficiency, desire of parents, and presence of possible favorable factors in a patient.
Keywords: STAT1, gain-of-function mutation, bone marrow transplantation, mucocutaneous candidiasis.

Резюме

Не так давно была описана мутация с усилением функции в STAT1. Эта мутация часто сопровождается клиникой тяжелого иммунодефицита. Применяемые в лечении таких пациентов антибактериальная и противогрибковая терапии не всегда эффективны. Некоторым пациентам проводилась трансплантация костного мозга с варьирующей эффективностью. Остаются неопределенными показания к трансплантации костного мозга при данной патологии. Это создает трудности для врачей и пациентов в принятии решения о трансплантации костного мозга. В данной работе мы описываем случай успешной трансплантации гемопоэтических стволовых клеток периферической крови пациенту с мутацией GOF в STAT1. У мальчика 1 года и 8 месяцев с мутацией GOF в STAT1 наблюдалось рецидивирующее течение кандидозной инфекции (эзофагит, стоматит), повторяющееся поражение легких, рецидивирующая пневмония со слабым ответом на антибактериальную и противогрибковую терапию. Рецидивирующие инфекции привели к задержке физического развития пациента. У него был выявлен клеточный иммунодефицит (снижение CD4+ Т-лимфоцитов). Неумолимое течение инфекционного синдрома, ухудшение качества жизни пациента и его семьи привели к решению провести трансплантацию костного мозга с согласия родителей. Возможными благоприятными прогностическими факторами успешной трансплантации костного мозга были ранний возраст, благоприятный вариант мутации GOF в STAT1 и наличие родственного донора. Пациент выжил, однако, в процессе трансплантации наблюдались осложнения в виде острой и хронической реакции «трансплантат против хозяина» (РТПХ). Произошло восстановление иммунитета, и инфекционный процесс не проявлялся. Пациент стал активным и в настоящее время в своем физическом развитии не отличается от сверстников. Решение о трансплантации при GOF в STAT1 должно приниматься в каждом случае индивидуально с учетом тяжести иммунодефицита, желания родителей и наличия потенциально благоприятных факторов для ее исхода у пациента.

Ключевые слова: STAT1, мутация с усилением функции, трансплантация костного мозга, кожно-слизистый кандидоз.

■ INTRODUCTION

Recently (2011, 2012) two groups of researchers independently established heterozygous signal transducer and activator of transcription 1 (STAT1) gain-of-function (GOF) as a reason of T-helper 17 (Th17) deficiency and autosomal dominant chronic mucocutaneous candidiasis (AD-CMC) [1, 2]. These mutations lead to inability of STAT1 dephosphorylation, hyperphosphorylation, increase of the linkage with DNA and GOF on STAT1 signals transmission. Moreover, a characteristic feature of patients with AD-CMC is a deficiency in Th17 responses, which is believed to be an immunological cause of muco-fungal infection. GOF mutations in STAT1 cause susceptibility to a number of infections, autoimmunity, impaired immune regulation and combined immunodeficiency. The manifestations of the disease can be mild or severe and life-threatening [3].

The standard of care for patients with STAT1 GOF mutations usually consists of supportive care options, including antimicrobial prophylaxis, alone or in conjunction with immunoglobulin replacement therapy, especially for patients with recurrent respiratory tract infections, with or without antibody deficiency [4–6].

Oral therapy with ruxolitinib, a Janus 1/2 (JAK1/2) kinase inhibitor that attenuates STAT1 activation by cytokine receptors, has also proven to be a viable alternative in combating disease complications including mucosal candidiasis and autoimmune diseases [7, 8]. However, these treatment options can't restore the immune deficiency.

Since these mutations have only recently been identified, a small number of patients have been reported in whom bone marrow transplantation (BMT) is accepted as a definitive treatment. Unfortunately, more than half of the registered patients died after transplantation due to multiple complications, most likely related to late decision or poor patient selection for BMT [4, 9, 10].

In describing two cases of heterozygous STAT1 GOF mutations mimicking combined immunodeficiency (CID) who were treated with hematopoietic stem-cell transplantation (HSCT), the authors concluded that HSCT could be an alternative treatment option for selected patients with mutant STAT1 GOF with progressive life-threatening disease not responding to conventional therapy [11].

Until now, a small number of patients underwent HSCT with mixed results, making the recommendation for this therapy inconclusive [4, 9, 12–14].

The international research group on STAT1 GOF has published five cases on transplanted patients with AD STAT1 GOF mutations. Only two of them are currently alive without serious complications [4]. In the study by Leiding et al. six patients (40%) survived in the transplant cohort. Complications causing morbidity and mortality included secondary graft failure, infections, and bleeding. The main problem with HSCT in patients with STAT1 mutation is the high incidence of secondary graft failure, the cause of which is not fully understood [14].

The publication on behalf of the Working Group on Congenital Errors of the European Society for Blood and Bone Marrow Transplantation and the Consortium for the Treatment of Primary Immunodeficiency Disorders collected data from an international cohort of 15 patients with GOF-STAT1 mutations who underwent HSCT using various conditioning regimens and donor sources. This multinational cohort of 15 patients represented the largest population of GOF-STAT1 mutated patients undergoing HSCT. The cohort consisted of 9 men and 6 women, ranging in age from 13 months to 33 years old at the time of transplant. Indications for HSCT were severe clinical manifestations, including recurrent infections, autoimmunity, immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX)-like symptoms resistant to drug therapy, hemophagocytic lymphohistiocytosis (HLH) or CID. Data show that HSCT in patients with GOF-STAT1 mutations is curable, but carries a significant risk of secondary graft failure and death [14]. This work also noted that most of the transplanted patients had mutations DBD (M390T, N397D, T385M, N397D, S466R, C324F), while the rest had helix domain mutations (D165G, R274W, R274Q, D292E, I294T, H328R), which, possibly, reflects the more severe course of the disease in patients with DBD mutations, for whom HSCT may be considered as an earlier therapeutic option. All 5 survivors with donor chimerism from 95% to 100% established complete restoration of immunity and complete reversal of immunodeficiency and resolution of infectious and autoimmune manifestations. Only the age at the time of transplantation as a good prognostic factor reached statistical

significance. Disease like IPEX and mutation resulting in T385M were favorable factors; however, patients with these characteristics underwent transplantation at a younger age. These data suggest that HSCT may be considered curative, especially if performed early in patients with GOF-STAT1 mutations with severe phenotypes including those with symptoms similar to IPEX, CID, serious life-threatening infections and severe autoimmunity. The data indicate that HSCT may be curative for patients with GOF-STAT1 mutations. With full restoration of immunity, the manifestations of the disease disappear quickly and forever [14].

Consequently, the accumulation of additional HSCT results in patients with STAT1 GOF mutations can provide valuable information relevant to the management of this disease.

■ CASE REPORT

The male patient was born from the third pregnancy with a weight of 3900 g, height 56 cm. He was vaccinated against hepatitis B and BCG vaccine. He has a brother and sister who are healthy.

Episodes of oral candidiasis from the age of one month were reported. From the age of eight months oral candidiasis (stomatitis) became permanent. From one month of age, the child has recurrent bronchopulmonary infections, which required hospitalization every other month. Vomiting (1–2 times per day) appeared from the age of four months. Antifungal and antibacterial therapy had a weak or short time effects. Regression of motor skills was detected. The boy stopped walking and needed support while sitting. Child almost didn't gain weight. The weight was 7500 g at the age of one year. At 15 months of age the boy was administered for pediatric immunologist consultation. The boy was admitted to the clinic in serious condition: respiratory failure, constant cough, wheezing on both sides and crackling in the lower parts on the right. Vomiting up to 6 times a day with thick mucus was reported. Sluggishness, poor appetite, decreased physical activity (swaying while walking), weakness, lethargy, slowness of movement, physical development retardation. Candidal infection – massive whitish thrush on oral mucosa and erythematous plaques with macerated surface was located on the skin around the mouth and anus.

A chronic inflammatory process in lungs with symptoms of hyperpneumatosis on X-ray, catarrhal endobronchitis on bronchoscopy, esophageal candidiasis and high gastroesophageal reflux on esophagogastroduodenoscopy was diagnosed. A significant growth of Candida in culture from oral and esophageal mucosa was detected. Microorganisms were not detected in blood culture.

Changes in cellular immunity were present with decrease of CD3+T-cells (1752/μl, normal ranges: 2100–6200/μl) because of CD3+CD4+ T-cells – 762/μl, normal ranges: 1300–4300/μl, decrease of IgA – 0.29 g/l (normal range – 0.4–1.7) but IgG – 13.59 g/l (normal range – 3.5–13.6) and IgM – 1.15 g/l (normal range – 0.3–1.9) were in normal ranges.

Follow-up immunologic tests revealed fluctuation of CD3+CD4+ cells absolute counts (762–910/μl, normal ranges: 1300–4300/μl).

Exclusion of HIV was needed because of decreased CD3+CD4+ cells.

It was also important to exclude tuberculosis because the boy with combined immune deficiency was vaccinated with BCG after delivery.

Tuberculin skin test was negative. When the child was admitted under our supervision, the examination for tuberculosis was not carried out, but clinically this diagnosis was unlikely.

Recurrent infections with a variety of pathogens leading to significant morbidity suggested combined immunodeficiency, chronic mucocutaneous candidiasis, or Mendelian susceptibility to mycobacterial disease

Pathogenic variant was detected during genetic examination. c.1154C> T (p.Thr385Met), was identified in STAT1. STAT1gen is associated with autosomal dominant chronic mucocutaneous candidiasis due to increased functions STAT1 (gain-of-function). Pathogenic variant in STAT1, c.1154C> T (p.Thr385Met) in family members (brother, sister, mother and father) was not found.

Treatment with piperacillin-tazobactam, linezolid and intravenous voriconazole had short-time positive effect. Prophylaxis antifungal therapy was prescribed: fluconazole (in syrup or tab.) 100 mg/day 1 time a day under the control of a regional pediatric immunologist. Continued with sulfamethoxazole-trimethoprim in the prophylactic dose 2.5 mg TMP/kg/day – ½ tsp. 1 time a day for 3 months. Amoxicillin-clavulanate in a dose of 320 mg/day – 4 ml of syrup (160 mg) twice a day. Therapeutically and prophylactic prescriptions had only temporary effect.

At the age of 20 months in view of uncontrolled severe lung damage, oral-esophageal candidiasis resistant to treatment, changes in immunity corresponding to combined immunodeficiency (CID), the patient's generally poor quality of life, the question arose of performing bone marrow transplantation (BMT). The decision on the choice of BMT was difficult, given that with immunodeficiency as a result of gain-of-function mutations in STAT1, there is no consensus on the use of bone marrow transplantation as a treatment due to the high mortality of such patients with it. At the same time, the data that the survivors after BMT with gain-of-function mutations in STAT1 completely underwent reconstitution of immunity, was in favor of BMT. The decision was made jointly with the patient's parents, who, despite all the risks, insisted on BMT because of the poor quality of life of the child and the whole family and the lack of hope for improvement.

The donor should be the boy's sister, who has a complete HLA compatibility with the consent of the parents, BMT is planned to be made by children's oncohematologists/transplantologists.

The child was hospitalized in the BMT department at the age of 22 months. The condition at the time of hospitalization was moderate to severe, due to the underlying disease, respiratory failure of the first degree, protein-energy deficiency of the second degree, moderate deficiency anemia.

Systemic antibacterial (meropenem), antifungal therapy (voriconazole), substitution intravenous human immunoglobulin 10%, partial parenteral nutrition, therapy with parenteral iron, erythropoietin was prescribed in preparation for allo-hematopoietic stem cell transplant (HSCT).

The child's condition was stabilized. Almost complete resolution of pulmonary symptoms (reduction of breathing rate to normal, normalization of the auscultatory picture) was achieved. Eliminated protein-energy deficiency by partial parenteral and correction of enteral nutrition (added 1.6 kg in weight). Anemia is adjusted from moderate to mild.

A comprehensive pre-transplant examination of the patient and the donor. There were no absolute contraindications to allo-HSCT.

Table 1
Transplant procedure and complications

Parameters	Patient	Parameters	Patient
Age at HSCT	22 month	Engraftment	ANC, PLT D+15
Source of donor	MSD, female PBSC	GvHD prophylaxis	CsA, Mtx
CD34+ count	5×10^6/kg	Transplant releated complication	No
CD3+ count	11×10^7/kg	Acute GvHD	Engraftment syndrome: fever, pulmonary edema, skin rush (D+9); Acute GvHD (fever, skin, lung?) (D+35)
Conditioning regimen	Treo/Flu/Thio+G-CSF +ATG +Rituximab	Chronic GvHD	Skin, gastrointestinal tract, lung? Autoimmune colitis?

Somatic status of the patient, before the procedure of allo-HSCT, on the Lansky scale was 70% [15].

Conditioning: Treosulfan / Fludarabine / Thiotepa + ATG "Timoglobulin" 5 mg/kg + rituximab 100 mg/m^2 + G-CSF 10 μg/kg/d on days -8, -7, -6, -5, -4.

Anti-thymocyte globulin (ATG) is included in the conditioning given the high risk of developing acute GvHD (female donor, graft – peripheral blood stem cell, large group incompatibility – blood group of patient A (II) Rh (positive), donor AB (IV) Rh (positive).

Rituximab is used to prevent the development of post-transplant lymphoproliferative disease (the patient had asymptomatic EBV viremia, EBV was detected in the bronchoalveolar fluid).

Peripheral blood stem cell was used as a source of stem cells.

Allo-HSCT (Day 0) – 110 ml of peripheral blood donor hematopoietic stem cell concentrate was transfused – without complications. The amount of transfused CD34+ – 5.0×106/kg, CD3+ – 11.0×107/kg, CD56+ / CD3– 2.5×108/kg body weight of the recipient.

Prevention of GVHD:

1. Cyclosporine (CsA) 1.5 mg/kg 2-hour infusion 2 g/day (daily dose 3 mg/kg/day) starting from day -1 while maintaining serum levels of 100–150 ng/ml.
2. Methotrexate 10 mg / m2 i.v., on days +1, +3 and +6.

Engrafts 18.07.19 (Day +15): -platelets; -neutrophilic; -erythrocytic.

Day +20: change of blood group to donor's AB (IV).

The graft reaction against the host had a recurrent course, with damage to the skin, intestines, lungs (biopsy was not performed), with the formation of dependence on steroids. The cumulative dose of steroids is 2070 mg/m^2.

Methylprednisolone therapy was completely discontinued on Day + 169 due to the development of severe side effects (morbid obesity, BMI >30). Oral treatment with budesonide was continued (D + 126).

Despite the complete abolition of methylprednisolone, dietary adjustment in the patient remained obese with a tendency to progressive weight gain.

Additional examinations were performed (fasting and postprandial glucose, C-peptide, homeostasis model assessment index, insulin, adrenocorticotropic hormone test, daily urine for cortisol, thyroid stimulating

hormone, T4, thyroperoxidase antibodies. After careful evaluation of the anamnesis, clinical picture, results of additional examination methods the situation is regarded as steroid-induced obesity associated with the systemic effects of budesonide.

From March 21, 20 – a slow gradual withdrawal of budesonide was started. Against the background of the last decrease in the dose of budesonide (from 4.04.20), the patient developed clinical manifestations of steroid withdrawal syndrome: refusal to eat, muscle weakness, vomiting, tendency to hyponatremia. Increasing the dose of budesonide had no effect. From 06.04.20 – started replacement therapy with hydrocortisone intravenously, with subsequent transition to oral administration.

On the combined immunosuppressive therapy (cyclosporine A + mycophenolate mofetil) the patient had the symptoms of GVHD (rash, itchy skin, anorexia, changes in the nature of stools). Given the complex of factors (term after allo-HSCT, the nature of the underlying disease, the inability to continue steroid therapy, recurrent and wavy course of GHVD, which significantly reduced quality of life, extended hospital stay, posed potential risks to the patient's health in the future) immunosuppression therapy was modified: D + 335 added ruxolitinib 5 mg/day in 2 doses.

21 days after the start of ruxolitinib therapy, the resolution of the above-described manifestations of HRT was reached. From 17.07.20 the dose was reduced to 2.5 mg/day due to myelotoxicity III (according to the WHO scale), which required replacement transfusions of blood products.

Cyclosporine A was canceled at D + 387, MMF – at D + 452.

At the time of writing D + 579 the patient remains alive. Reconstitution of T lymphocytes occurred (Table 3). The patient continues treatment with ruxolitinib due to chronic GVHD and hydrocortisone replacement therapy with gradual dose reduction. There are no signs of infection, but against

Table 2
Monitoring of chimerism

Chimerism (FISH)	+34	+62	+99	+174	+240	+365
Peripherial blood	99.79%	99.1%	99.5%	98.5%	99%	99%
Bone marrow	99.18%	99.5%	99.7%	96.4%		

Table 3
Monitoring of immune reconstitution

Subpopulation of lymphocytes ($\times 10^9$/l)	Patient range							
	Before HSCT	D+ 36	D+ 99	D+ 204	D+ 274	D+ 334	D+ 467	D+ 537
General Count	4.1	1.3	1.7	2.0	2.9	2	3.2	4.6
B-cells	1.7	0	0	0.0004	0	0.18	0.48	0.6
T-cells	2.3	1.24	1.6	1.84	2.8	1.74	2.69	3.9
CD3+/CD4+	1.2	0.39	0.8	0.5	0.6	0.42	1.31	2.0
CD3+/CD8+	0.9	0.69	0.4	0.96	1.8	1	1.02	1.15
NK-cells	0.1	0.05	0.08	0.2	0.15	0.09	0.06	0.17
CD4/CD8	1.4	0.6	1.9	0.5	0.3	0.4	1.3	1.3

the background of antifungal and antiviral prevention. Immunoglobulin replacement therapy is periodically performed according to the patient's serum immunoglobulin levels.

He caught up with his age height of 93 cm, and has a corresponding body weight of 15,800 g. The parents have no complaints about the child's condition, they note an improvement in the condition compared to the condition before BMT.

Chimerism and immune reconstitution monitoring data are shown in Tables 2 and 3.

The table 2 indicate complete donor chimerism in the patient 1 year after allo- HSCT.

■ DISCUSSION

We present a new case of the SCT with gain-of function mutations in STAT1. The decision on the choice of BMT was difficult, given that with immunodeficiency as a result of gain-of-function mutations in STAT1, there is no consensus on the use of bone marrow transplantation as a treatment due to the high mortality of such patients with it. At the same time, the data that patients with gain-of-function mutations in STAT1 who survived after BMT completely underwent reconstitution of immunity, inclined to carry out BMT. The decision was made jointly with the patient's parents, who, despite all the risks, insisted on BMT due to the poor quality of life of the child and the whole family and the lack of effect from antibiotic therapy and prevention and hope for improvement.

Among the factors that, according to the literature, are associated with successful BMT, the most important is the early age of the patient. In our case, the diagnosis of PID was established at a fairly early age. In Ukraine, the awareness of doctors regarding primary immunodeficiencies has increased as a result of educational programs within the framework of the Central-Eastern J-project [13, 16]. Moreover, a mutation found in a patient in the DNA-binding domain (DBD) STAT1 c.1154C>T, p.T385M is included in the list of described mutations with a favorable course of BMT [11, 13, 14].

In addition, stabilizing the patient's condition before transplantation and anticipating common complications after transplantation for early intervention also contributed to survival.

At the stages of allo-HSCT, the main problem for this patient was the development of acute and chronic GVHD. The following adverse factors were present in the development of this complication: the sex of the donor (female), the source of hematopoietic stem cells – peripheral blood.

GVHD had a recurrent and progressive course, significantly reduced the quality of life of the patient, extended the period of hospitalization, led to an increase in the frequency of treatment related adverse events – syndrome of exogenous hypercortisolism (including obesity), acute adrenal insufficiency.

Standard therapy of GVHD (steroids, calcineurin inhibitors, mycophenolate mofetil) in this case was not successful, due to the formation of the patient's dependence on steroids and the development of severe side effects from them (morbid obesity). Therefore, ruxolitinib was chosen as the drug of choice in this clinical situation, according to the latest literature data.

Resolution of chronic GVHD phenomena was reached in 21 days. It has become possible to reduce the amount of immunosuppressive therapy (cancellation of cyclosporine A and MMF) and thus achieve the desired immune reconstitution.

The patient tolerates the drug satisfactorily, with side effects there was hepatotoxicity of the first degree and myelotoxicity of the III degree according to the WHO scale.

Cases of graft insufficiency and graft rejection described in the literature for this cohort of patients were not observed in this clinical situation. Sufficient levels of donor chimerism (FISH determination) were observed throughout the observation period, but in our BMT center there is no possibility to determine chimerism in subpopulations of lymphocytes.

In conclusion, our communication can help other patients, families, and clinicians decide on BMT for subjects with STAT1GOF mutations and severe clinical course despite conventional therapy.

The decision to perform allo- HSCT for each individual patient should be considered, taking into account the benefit/risk balance.

Data Availability Statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, to any qualified researcher.

Ethics Statement

The studies involving human participants were reviewed and approved by Ethics Committee of the OKHMATDYT. Written informed consent to participate in this study was provided by the participants' legal guardian/ next of kin.

Authors' contribution

Lysytsia O., Stryha N. – bone marrow transplantation and writing the paper; Beglaryan S., Shadrin O. – follow up and treatment of the patient; Chernyshova L. – treatment coordination, differential diagnostic workup, treatment of the patient, writing the paper.

All listed authors have made a substantial, direct and intellectual contribution to the work and approved it for publication.

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Conflict of interest

The authors declare no conflict of interest.

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