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ORPHAN DISEASE: A RARE CASE OF MALIGNANT OSTEOPETROSIS

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Abstract

Reports on clinical cases of orphan pathologies, as autosomal recessive type of infantile malignant osteopetrosis, have a great practical importance for scholars.

Osteopetrosis may already manifest itself in utero. In early childhood, there is a classic triad of symptoms: increased bone density and fragility, severe anemia. Diagnostics and allogeneic hematopoietic stem cell transplantation at the age of up to 1 year can be cured and significantly increase life expectancy.

Bone marrow transplantation is only treatment that has been proven to significantly alter course of autosomal recessive type of osteopetrosis. Inspide of successful transplantation may orthopaedic, dental problems and their vision rarely significantly improves, however haemopoietic potential is restored and the long term prognosis is favourable.

Herein we report a case of patient diagnosed with osteopetrosis and underwent allogeneic hematopoietic stem cell transplantation, with no prior determination type of mutation.

Complexity of case: late diagnosis autosomal recessive type of osteopetrosis (at 3.1 years), despite characteristic early clinical manifestations, a protracted preparatory period associated with search for an unrelated donor and COVID-19 pandemic, for allogeneic -hematopoietic stem cell transplantation performed at the age of 4.3 years.

In resulting, was engraftment of bone marrow transplant, with restoration hematopoietic function, but with preserved neurological and physical disabilities in a form of psychomotor development retardation.

Allogeneic hematopoietic stem cell transplantation led to restoration hematopoietic function of the graft in this case of late diagnosis osteopetrosis.

Keywords: *orphan, osteopetrosis, transfusion, transplantation*

Introduction

Autosomal recessive osteopetrosis (ARO) is a genetically heterogeneous rare skeletal disease with failure of osteoclast resorption. Incidence of 1 in 200-250 thousand newborns [*Bliznetz E.A, et al, 2005; Burya A.E. et al, 2019]*. Among people, due to living in geographically isolated regions such as Pakistan, Sweden, Costa Rica and certain regions of Russia (Chuvash and Mari Republics) and those who have incestuous relationship the incidence of ARO is 1 in 3500-14000 newborns. The average life expectancy is 3 years with no pathogenetic treatment. Life expectancy of patients is 6 years in 70% of cases, mortality occurs in early childhood, the rest have a poor quality of life, life expectancy is 10 years [*Sobacchi C. et al, 2001]*.

ARO units a group of primary bone sclerosis, manifested by complete disappearance and deficiency of bone marrow (BM), pancytopenia, impaired mineral homeostasis, hypercalcemia, psychomotor retardation, hepatosplenomegaly, blindness, deafness and frequency, decreased immunity [*Wilson C J et al, 2000; Sobacchi C. et al 2001; Vomero A. et al, 2019*].

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Clinical manifestations begin in early childhood; as an infantile and malignant autosomal recessive osteopetrosis. Classic triad symptoms are observed: increased bone density, fragility and anemia. It is characterized by increased bone density due to increased resorption, which leads to thickening bones, narrowing and completes disappearance of bone marrow canals, disruption mineral homeostasis [*Wilson C J et al, 2000*]. Visual loss, caused by bony sclerosis of optic nerve at the level optic foramina, is progressive and almost always occurs within first year of life. Psychomotor development lags, characteristic facial features, bone marrow failure, hypercalcemia, pancytopenia in form of anemia, leukopenia and thrombocytopenia occur. Hepatosplenomegaly due to extramedullary hematopoiesis leads to development of blindness, deafness and paralysis facial nerve, intracerebral hemorrhages due to thrombocytopenia, frequent infections due to decreased immunity [*Sobacchi C. et al 2001; Ismailova G.et al, 2018; Shokebaev A. et al, 2018; Ismailova G. et al, 2017; Vomero A. et al, 2019*].

Patients with ADO have a milder form of mutation in the chloride transport gene ClCN7 than that seen in the more severe forms of infantile osteopetrosis, although other genes may be involved. Decreased bone resorption presumably results from impaired acidification. The autosomal recessive type of osteopetrosis is due to the variable spectrum of mutation types: TCIRG1; CLCN7; OSTM1; RANKL; RANK; CLCN7; PLEKHM1; CAII; Kindlin-3; CalDAG-GEF1 and CTSK [*Bliznetz E.A. et al, 2009; Zhang X.Y, et al 2017*].

Abnormal deformation of bone structures develops, in form of macrocephaly, frontal bulges, dental anomalies, choanal stenosis and hydrocephalus. Due to violation of longitudinal growth of bones, there is a low growth of varying degrees. Due to excessive compaction bones skull, bone structure expands, which leads to closure openings skull and disruption passage of blood vessels and nerves. Diagnosis is based on the presence skeletal radiographs, which include: diffuse sclerosis bones of skull, spine, shoulder girdle, upper limbs, pelvic girdle and lower limbs; defects in bone modeling in the metaphyses tubular bones, in form a funnel-shaped deformation of the "Erlenmeyer flask" type, and characteristic antireflection stripes; focal sclerosis base of skull, pelvis and vertebral end [*Sobacchi C.et al, 2013; Burya A.E. et al, 2019; Radygina S.A., et al, 2019*].

To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

Transfusion dependence before the first month of life is a sign of severe ARO and therefore a poor prognostic sign. This leads to massive compensatory extramedullary hepatosplenomegaly. Patients who are most dependent on blood transfusion and who have extramedullary hematopoiesis require bone marrow renewal. It is advisable to perform bone marrow transplantation before the primary blood transfusion in the first year of life [*Wilson C J et al, 2000; Sobacchi C.et al, 2013; Burya A.E. et al, 2019; Radygina S.A., et al, 2019*].

Case presentation

A retrospective analysis of a case "malignant" osteopetrosis in a 6.2-year-old girl, who was first diagnosed at the age 3.1 years when she was referred to the Children's infectious diseases hospital. She was admitted for fever, cough, hydrocephalus and such neurological symptoms as macrocephaly, no verbal and non-verbal communication, aggressive reaction, and moving disorders. Her birth weight was 4500 grams, height was 54 centimeters Apgar scale 7-8, hypostatura Z-score 3 (85%) (Table 1). The girl was born from third birth; the pregnancy was hard, as mother had acute respiratory infections, breech presentation, "large" fetus.

On the plain chest X-ray, there were signs of bronchopneumonia, total osteosclerosis, as the cause of suppression hematopoiesis and severe aplastic anemia. Osteopetrosis (Figure 1).

Results of analysis showed considerable reductions: Hb 58 *g/L*, RBS $2.2x10^{12}$/ *L*, PLT $100x10^{3}$ µ/L and ESR 40 *mm/h*. The neurological status was low: macrocephaly, no vision; hears; does not answer questions, aggressive reaction; does not sit or walk on its own. Signs of protein-energy malnutrition, height is 90.2±0.3 *cm*, growth deficit (-) 1.3 *cm* relative to the lowest threshold, p<0.0001, CI95% [89.9; 90.4], weight was 12.8±0.4 *kg*.

Table 1

Timeline table

Age	Hospitalized with diagnosis	Healing tactics
2 (months)	Intrauterine infection (IUI) cytomegalovirus (CMV), thrombocytopenia, anemia	Pathogenetic therapy
4 (months)	Bilateral acute otitis media (BAOM). IUI CMV. Anemia	
4.5 (months)	Acute Bacterial Meningitis. IUI CMV. Anemia	
6 (months)	BAOM. IUI CMV Anemia	
1.4 (y/o)	Post-infection hydrocephalus, lower paraparesis, optic atrophy. Psychomotor Development Retardation (PDR)	Ventriculoperitoneal shunt
2.7 (y/o)	C2 Arch fracture	Immobilization, vitamin D3 and calcium
3.1 (y/o)	Acute pneumonia. Osteopetrosis.	Antibacterial and antiviral therapy
Monthly from 3.2 to 3.7 (y/o)	Osteopetrosis. Secondary thrombocytopenia	Hemotransfusion, Exjade
From 3.8 to 4.2 (y/o)	Osteopetrosis. Pre allogeneic Hematopoietic stem cell transplantation (HSCT).	Pathogenetic therapy Hemotransfusion. Exjade
From 4.2 to 4.4 (y/o)	Osteopetrosis. Allogeneic HSCT.	Allogeneic HSCT. Hemotransfusion. Exjade. Tacrolimus.
From 4.4 to 4.8 (y/o)	Osteopetrosis. Post allogeneic HSCT.	Pathogenetic therapy, Hemotransfusion. Exjade. Tacrolimus.
from 4.8 (y/o) to today	Osteopetrosis. Post allogeneic HSCT.	Tacrolimus

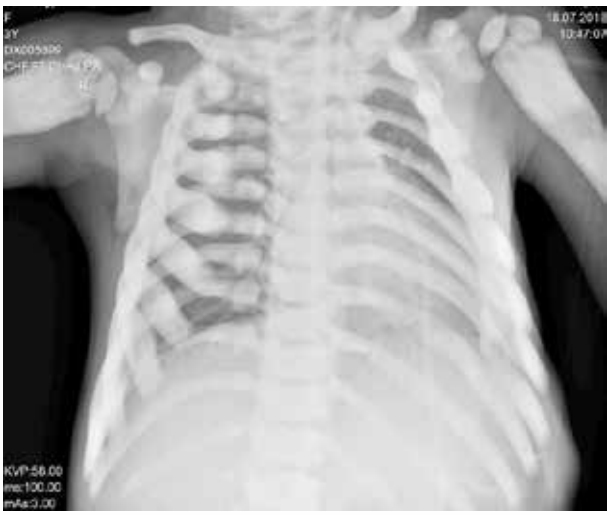

Figure 1. *Patient 3.1 years old. Plain chest x-ray. Erlenmeyer flask deformity is visualized with a characteristic enlightenment band in left humerus. Extended costochondral joints. There is no BM differentiation. Total osteosclerosis.*

Geneticist consultation: clinical and radiological signs of ARO.Hypercalcemia 12.4±1.9 *mg/dl*, P=0.0084, CI95% [10.9; 13.8], with normalization after infusion Pamidronat, Lasix, Prednisone. The high risk developing sepsis: procalcitonin (PCT) 4.28 *mg/L* and C-reactive protein (CRP) 12.54 *mg/L*, after antibacterial, antiviral, immunostimulating therapy, is reduced to a dubious risk. Increased alanine aminotransferase (ALT), aspartate aminotransferase (AST) and AST/ALT as a result of CMV hepatitis (Table 2). Computed tomography of head showed narrowing cortical grooves, cerebellar sheets, cisterns area and 4th ventricle. A narrowing is noted in the left lateral ventricle, possibly due to excessive shunt work. Diffuse sclerosis bone structures, shunt catheter in the left lateral ventricle. There is no pneumatization of sinuses and temporal bone. Clinical correlation with spasms as a consequence spastic epilepsy.

Table 2

Main laboratory parameters

Blood parameters	M±SD	n	P-value	CI95%
Ca *(mg/dl)*	9.0±0.4	60	<0.0001*	[8.8; 9.1]
P *(mg/dl)*	3.9±0.9	4	0.1961	[4.9; 12.9]
ALP† *(U/L)*	179±7.1	2	0.0205*	[115.2; 242.8]
PCT *(mg/L)*	0.7±0.1	4	0.0106*	[0.6; 0.8]
CRP *(mg/L)*	1.0±0.9	58	0.4500	[0.65; 0.76]
ALT *(U/L)*	39.2±10.1	63	<0.0001*	[36.6; 41.8]
AST (U/L)	129.6±45.5	63	<0.0001*	[118.1; 141.0]
AST/ALT	3.4±1.4	63	<0.0001*	[3.0; 3.8]

Notes: ** Statistically significant difference*
† Alkaline phosphatase

Ultrasound of abdominal cavity revealed hepatosplenomegaly and hepatosteatosis, isoechoic solid formations in para-iliacale areas on both sides – conglomerates lymph nodes associated with extramedullary hematopoiesis.

The patient is worried about snoring and noisy breathing due to progressive osteosclerosis and choanal obliteration. There is a blood transfusion dependence (Figure 2).Test for Human Leukocyte Antigens (HLA) typing of donors among relatives is not revealed. According to results of 4-stage HLA typing, 9 out of 10, in September 2019, at the age of 4.3 years, patient underwent allogeneic HSCT of BM CD34+ cells with a cellularity 10x10^6/*kg* from a matched unrelated donor of opposite sex.

A skin rash was noted as a graft-versus-host reaction in early post-transplant period; from 12th day of received prednisone and tacrolimus. Assessment of leukocyte chimerism by fluorescent in situ hybridization was performed monthly is 98%.

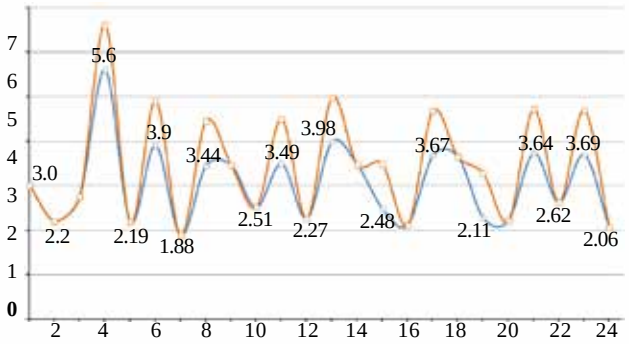

Figure 2. *Diagram changes in red blood cells level relative to blood transfusion*

In the late period, hypofunction the graft noted, and therefore, received hemotransfusion of B(III) Rh(+) suspensions of PLTs 38 and RBCs 53 bags, until complete engraftment the graft confirmed by leukocytes at 35th and platelets at 97th days.

At the time examination - condition is stable, closer to satisfactory, 2nd year after allogeneic HSCT. Hematological blood parameters within the age norm: RBC (3.9±0.9) x10^9/*L* and WBC (6.7±1.9) x10^6/*L* without hemotransfusion correction.

Physical development "below a healthy weight" BMI-for-age is at the 3rd percentile: weight is 16 *kg*, height is 110 cm. Respiration is sonorous wheeze, respiratory rate 18 breaths per minute and heart rate (pulse) 82 *bpm*. Muffled heart sounds; oxygen saturation level is 97%. Delay in changing milk teeth (absent) to permanent teeth that makes difficult eating solid food. Neurological status showed slight improvements (Table 3).

Discussion

Osteopetrosis is characterized by disorders in formation of bone structures and complete disappearance of bone marrow hematopoiesis, and neurological deficits, atrophy the cranial nerves, in 75% cases, atrophy the optic nerve. ARO signs can appear in the womb [*Chávez-Güitrón L.E.et al, 2018; Burya A.E. et al, 2019; Radygina S.A., et al, 2019*].

Luis E. Chávez-Güitrón et al. reported that ARO could be suspected on the basis of pancytopenia, hepatomegaly, impaired growth, and could be diagnosed osteopetrosis based by disorders of calcium and phosphorus metabolism and increased bone density. Allogeneic HSCT of BM at the age up to 1 year can cure ARO and significantly increase a life expectancy [*Chávez-Güitrón L.E.et al, 2018*].

In our clinical case, the diagnosis was established when the patient was 3 years old, despite the presence of early clinical manifestations of osteopetrosis: thrombocytopenia, anemia, hepatosplenomegaly, decreased immunity, hydrocephalic syndrome and PDR.

Table 3

Psychomotor development

Indicators Before		Allogeneic HSCT	
		Before	After
Harmony	Harmonious development	Disharmonic	
Motor skills:	Sit, stand	With support of	On one's own
	Walk		With support of
	Hold your head		On one's own
Thin	Pinch grip	Weakly	Expressed
	Play with toys		Interested in
Coordinated	Purposeful movements		Expressed
Speech	Understanding	Simple words	Phrases
	Pronounces		Offers
	Sensory speech	Scarce	Answers questions
Focusing	Auditory	Low	Positive
	Spotting	Absent	
Social development	Hold a spoon	Not sure	Confidently
	Eat solid food	Weakly	Trying to
Conditionally	Learns parents	Adequate	
	Reaction to outsiders	Adequate	

Osteopetrosis has been developed due to a number of mutations: TCIRG1; CLCN7; OSTM1; RANKL; RANK; CLCN7; PLEKHM1; CAII; Kindlin-3; CalDAG-GEF1 and CTSK, but for some them effectiveness HSCT is questionable (CLCN7) or ineffective (RANKL and OSTM1 +) [*Sobacchi C, et al, 2013; Sobacchi C, et al. 2014; Vakhonina L.V. et al, 2017; Howaldt A, et al, 2020*].

Although, mutation in TCIRG1 occurs in >50% of ARO patients, it is characterized by low levels calcium and phosphorus [*Vakhonina L.V. et al, 2017*]. In our case, a mutation study was not performed [*Bliznetz E.A. et al, 2009; Zhang X.Y, et al 2017*].

Allogeneic HSCT of BM is effective at the age up to one year or before severe lesions BM and neurosensory consequences osteosclerosis [*Sobacchi C.et al, 2013; Burya A.E. et al, 2019; Radygina S.A., et al, 2019*]. The median cellularity HSCT for non-oncology patients is CD34+ 8.1×10^6/*kg*; hypofunction of graft may be noted during post-transplant period and requiring additional hemotransfusions [*Burya A.E. et al, 2021*].

In conclusion, clinical case showed a relatively positive clinical effect of allogeneic HSCT from a MUD, despite late diagnostic and therapeutic tactics of malignant osteopetrosis.

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