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An Episode of Moshkovitz Syndrome in an 11-year-old Child: a Clinical Observation

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Abstract

Moshkovitz syndrome, which is also called thrombotic thrombocytopenic purpura (TTP), is an extremely severe multimorbid pathology. TTP is characterized by a very aggressive course, requiring immediate initiation of treatment in the first hours of occurrence, because, without fast and properly selected therapy, the mortality rate approaches 100% regardless of age. The foundation of Moshkovitz syndrome is a sharp increase in platelet aggregation with the formation of thrombi consisting of platelets and von Willebrand factor in small vessels of organs. The target organs that are affected in the first place are the brain, lungs, and kidneys. There is a sharp development of thrombocytopenia, microangiopathic hemolytic anemia, and ischemia in the most important organs. It is difficult to diagnose the disease due to the absence of specific symptoms. The disease often develops suddenly against the background of full health and in most cases resembles ARVI. In children, TTP is very rare, and therefore it is difficult for clinicians to verify the disease and determine a therapy strategy. The article presents an analysis of a clinical case of an 11-year-old girl with Moshkovitz syndrome.

Disciplinary: Medicine.

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1 Introduction

The etiology and pathogenetic mechanisms of Moshkovitz syndrome have not been precisely investigated: there are different hypotheses and theories about the origin and development of pathology. According to its hematological and pathohistological features, the disease is close to systemic lupus erythematosus, Fisher-Evans syndrome, and hemolytic-uremic syndrome. Some attribute TTP to the group of laminopathies [1-3].

2 Literature Review

Since the beginning of the two thousandths, several important discoveries have been made, after which TTP became clearer. J.L. Moake and colleagues (USA) found large von Willebrand factor multimers in the plasma of four patients with recurrent TTP, they were similar in size to those secreted by megakaryocytes and endothelial cells, and contained in alpha–granules of platelets and corpuscles Weibel–Palade of endothelial cells. The hypothesis put forward explained the presence of macromolecules of this coagulation factor by the absence of protease or disulfide reductase in patients, which cleaves them [4].

H. Tsai (USA) and M. Furlan, R. Robles, B. Lämmle (Switzerland) published the results of studies in which they independently found that patients with TTP have a deficiency of metalloprotease, which reduces the size of von Willebrand factor multimers by splitting them. Subsequently, the enzyme was identified as ADAMTS–13 (A Disintegrin And Metalloprotease with ThromboSpondin type 1 motif). In general, antibodies in patients with Moshkovitz syndrome are found very rarely [5, 6].

Moshkovitz syndrome is characterized by the presence of "classic" pathological components: severe thrombocytopenia (platelet count <30x10g/l and the presence of hemorrhagic syndrome), microangiopathic hemolytic anemia (decreased hemoglobin (40-80 g/l), reticulocytosis, hyperbilirubinemia, increased lactate dehydrogenase), neurological disorders (impaired consciousness up to coma, headache seizures, various focal disorders), kidney damage (microhematuria, proteinuria, cylindric, nephrotic syndrome, acute renal failure) and fever. In 35% of cases with TTP, abdominal syndrome occurs in patients. The examination may reveal pallor of the skin and mucous membranes, purpura, jaundice, enlargement of the spleen, and an increase in blood pressure. The syndrome is based on a widespread lesion of small vessels with endothelial proliferation, fibrinoid necrosis, the formation of parietal, and obstructing fibrin and hyaline thrombi in the areas of damage. Fibrin is deposited first subendothelial, which is accompanied by swelling of the endothelium and narrowing of the vascular lumen. The passage of red blood cells through the narrowed lumen of capillaries, and repeated contact of red blood cells with pathologically altered vessels lead to fragmentation of red blood cells and intravascular hemolysis. The absence of complement in the walls of the affected vessels, in the glomerular basement membrane of the kidneys, and in intravascular thrombi, the frequent detection of only fibrin without immunoglobulin in the affected areas indicate, apparently, that the antigen-antibody reaction does not play a role in the triggering mechanism of the disease [7-10].

Despite the fact that it is difficult to establish a diagnosis (especially to do it quickly), the conclusion is based on clinical and laboratory indicators. Particular importance is attached to increasing the activity of lactate dehydrogenase in blood serum. Treatment of TTP has cardinal differences from other thrombovasculitis. Reduction of microthrombosis is achieved by the use of plasmapheresis with a large volume of freshly frozen plasma, antiplatelet agents, glucocorticoids, according to clinical indications, and transfusion of erythrocyte mass. Platelet infusions are not indicated. Indicators of the weakening of the microangiopathic process, indicating the successful therapy of TTP, are: a decrease in neurological symptoms, improved kidney function, increased hemoglobin levels, a decrease in the number of reticulocytes, schizocytes, and lactate dehydrogenase concentrations [11-17].

3 Method

As a clinical and laboratory picture of the Moshkovitz syndrome with successful therapy, a description of a clinical case of an 11-year-old child in the hematological and oncological department of the Russian Children's Clinical Hospital is presented.

4 Result and Discussion

Patient R., 11 years old, was taken to the hematological and oncological department of the Russian Children's Clinical Hospital on 05/25/15. Of the complaints, general weakness, fatigue, pallor, jaundice of the skin, hemorrhagic rashes, and irritability were noted.

Anamnesis: was born from the second pregnancy without pathology, the second urgent delivery. Body weight at birth is 3.4 kg. The body develops according to her age. The girl was vaccinated according to the calendar.

Table 1:. Hemogram indicators.

Date	RBC $*10^{12}$	HB, g/l	Reticulocytes, %o	Thrombocyte, $*10^9$/l	WBC $*10^9$/l	Band kernels %	Eosinophils, %	Segmental %	Lymphocytes, %	Monocytes, %	Normoblasts	ERS, mm/h
14.05	2.62	82	-	10	3.82	-	1	32	56	11		2
26.05	2.35	85	120	30	6.2	7	0	73	15	5		8
28.05	1.9	65	119	18	3.5	2	0	22	71	5		22
30.05	2.44	83	117	28	6.3	3	1	23	70	3		20
1.06	1.89	67	-	17	11.9	9	2	61	22	6	3:100	25
3.06	1.46	53	-	86	7.1	9	0	65	25	1		30
Moderate toxogenic granularity. Anisocytosis of erythrocytes, isolated schizocytes.												
5.06	2.13	76	-	114	9.7	3	0	58	35	4	6:100	10
7.06	2.78	99	-	70	12.8	6	2	62	24	6		71
10.06	2.94	102	-	21	6.4	4	0	36	55	5	-	70
14.06	2.77	95	139	34	10.2	5	0	61	27	7	-	67

The present disease began about three weeks before the day of hospitalization, when weakness, pallor, and jaundice of the skin, and hemorrhagic rashes on the lower extremities appeared. An outpatient examination revealed changes in the hemogram in the form of a decrease in the content of hemoglobin and platelets, and therefore the patient was hospitalized. During the examination in the hospital, the patient's condition was severe due to anemia, hemorrhagic, and intoxication syndromes. Body weight 27 kg, height 133 cm, the level of physical development is below average. Jaundice of the skin on a pale background, pallor of the sclera, hemorrhagic rash in

the form of petechiae, ecchymosis on the lower extremities and trunk. The sclera are subicteric. Peripheral lymph nodes (cervical, axillary, inguinal) are single, up to 0.5-1.0 cm in size, elastic consistency. Percussion over the lungs is a boxy shade of pulmonary sound, in the lower parts there is a dullness. Auscultation - breathing is hard, and weakened in the lower parts. The number of breathing movements is 24-26 per minute. The heart area is not visually altered. The boundaries of relative cardiac dullness within the age norm. Heart rate 112-120 per minute, blood pressure 110/65 - 140/80 mmHg. The abdomen is soft, painless. Liver + 1.0 cm, smooth edges, moderately elastic consistency. The spleen is located at the edge of the costal arch. A chair is formed. Urine is light yellow (dark brown color was observed several times). Neuropsychological development corresponds to age.

Laboratory data:

Blood type B (III), Rh - positive.

Blood test from 02.06.2015: plasma myeloperoxidase activity ADAMTS-13 - 8% of the activity level in the control plasma.

Blood test for the level of antibodies to the N-factor from 4.06.2015: 23%. Inhibitory antibodies against ADAMTS-13 (from 03.06.2015) – positive result.

A blood test for SLE markers from 4.06.2015: 1. Lupus anticoagulant – weakly present. 2. IgG antibodies to double-stranded DNN 11.6 units/ml (0-25) 3. IgG phospholipid antibodies – 5.85 units/ml (0-10) 4. IgM phospholipid antibodies – 3.12 units/ml (0-10) 5. Antinuclear antibodies (SS-A/Ro, SS-B/La, RNP70, Sm, RNP/Sm) – negative result. 6. Antibodies to β2-glycoprotein 1 IgG – 2.77 units/ml (0-5) 7. Antibodies to β2-glycoprotein 1 IgM – 1.26 units/ml (0-5) 8. Antibodies to cardiolipin IgG – 1.9 units/ml (0-10) 9. Antibodies to cardiolipin IgM – 1/ml (0-7).

Table 2: Biochemical blood analysis.

Date	ALAT, Units/l	ASAT, Units/l	Total protein, g/l	Albumin, , g/l	Total bilirubin, mcmol/l	Direct bilirubin, mcmol/l	K+, mmol/ L	Creatinine, mcmol/l	Urea, mmol/L	Glucose, mmol/L	Lactate dehydrogenase, Units/l
14.05	14	53	-	-	50,7	6,9	-	-	-	-	-
25.05	18.2	45.5	62.5	40.1	36.8	24.3	3.66	60.8	3.2	-	561.3
28.05	83.9	83.9	-	-	53.3	4.0	-	68.3	3.0	-	848.1
30.05	28.4	96.0	57.3	50.6	49.9	6.5	2.9	60.1	5.0	-	-
02.06	43.8	78.8	67.5	-	65.7	42.6	2.9	65.3	7.0	4.6	244.3
06.06	59.8	63.9	84.6	-	30.5	1.9	-	59.0	7.6	-	-
09.06	83.3	-	-	-	25.3	2.6	3.0	45.7	5.6	-	-
11.06	-	51.0	90.0	36.0	47.0	3.0	4.4	43.8	6.4	-	-
13.06	23.6	30.6	60.0	57.0	25.3	4.3	4.2	49.3	7.7	4.0	-
15.06	39.0	71.0	-	-	16.7	1.3	5.5	51.1	4.23	-	-

Coagulogram from 26.05.2015: fibrinogen - 2.73 g/l, PV - 26.8 seconds, prothrombin index - 54.7%, prothrombin time - 1.55.

Coagulogram from 02.06.2015: prothrombin index - 78.6%, fibrinogen - 4.44 g/l, international normalized ratio - 1.31

Coagulogram from 06.03.2015: prothrombin index - 85.2%, fibrinogen - 4.4 g/l, international normalized ratio - 1.24

Coombs test (direct and indirect) from 05.26.2015: negative result.

Bone marrow examination from 29.05.2015: on a myelogram, bone marrow punctate is rich in cellular elements. Blast cells - 0.8%. The megakaryocytic germ has narrowed. During the general examination of the preparations - single megakaryocytes without grounding.

Table 3:. General urine analysis.

Date	Colour	Transparency	Density	Protein in urine, g/l	White blood cells	Red blood cells	Cylinders	Salts	Mucus	Bacteria
26.05	straw yellow	Transp.	1018	-	0-2-1	-	-	urats	-	-
29.05	straw yellow	Transp.	-	0.34	2-2-3	3-3-3	-	urats	+	-
30.05	dark yellow	muddy	1014	1.740	6-8-7	14-12-15	hyaline, 1-1-1	oxalates, phosphates	+++	Large amounts
01.06	straw yellow	Transp.	1015	0.39	8-10-7	2-2-3	1-0-1	phosphates	++	-
02.06	straw yellow	Transp.	1011	1.55	2-0-1	12-11-10	-	oxalates	-	-
05.06	dark yellow	Transp.	1020	2.840	3-3-4	5-7-7	-	oxalates, phosphates	-	-
10.06	straw yellow	Transp.	1020	5.4	4-4-5	leached. large amounts	-	-	+	-
13.06	straw yellow	Transp.	1010	4.6	4-5-6	15-16-14 maintained	-	urats	-	-
15.06	yellow	Transp.	1017	3.68	1-0-1	3-4-3		phosphates	-	-

Urine test for bile pigments from 29.05.2015: the result is negative.

ECG from 26.05.2015: sinus rhythm, tachycardia 120 v min. The normal position of the electric axis. Incomplete Right Bundle Branch Block.

ECG from 01.06.2015: sinus rhythm, tachycardia, 125-130 v min. Vertical position of the electrical axis of the heart. Violation of ventricular repolarization.

ECG from 04.06.2015: sinus rhythm, 110 v min. The normal position of the electrical axis of the heart. Incomplete Right Bundle Branch Block. There is a slight positive trend since 1.06.2015: Violation of the processes of ventricular repolarization. Vertical position of the electrical axis of the heart.

ECG from 08.06.2015: Sinus rhythm, 77 in 1 min, the position of the electrical axis of the heart is normal. A variant of the norms.

ECHO KG from 27.05.2015: the size of the walls and cavities of the heart within the age norm. Pronounced mitral valve prolapse - 4.2 mm (grade I). interventricular septum, interatrial septum - solid. The contractile function of the myocardium is satisfactory.

ECHO KG from 02.06.2015: Conclusion: There is no valvular pathology. The contractile function of the myocardium is not impaired. There is no free fluid in the pericardium. There were no signs of intracardiac bypass surgery.

Chest X-ray diagram from 05.26.2015: pulmonary fields are transparent. The pulmonary pattern is moderately enhanced in the basal zones. The shadows of the roots are structural. The sinuses are free. The shadow of the mediastinum without features.

Chest X-ray diagram from 02.06.2015: enrichment of the pulmonary pattern in the basal and lower-middle zones. The structure of the roots is fuzzy. High aperture position. The sinuses are free. The waist of the heart is smoothed.

Ultrasound investigation of the abdominal cavity from 05.26.2015: the liver is 1 cm below the costal arch, the echostructure of the parenchyma is homogeneous, of medium echogenicity, the vascular pattern is preserved. The gallbladder is of normal size, deformed, the walls are compacted, the contents are homogeneous. Pancreas, spleen, lobes - the norm.

Ultrasound investigation of the abdominal cavity from 02.06.2015: liver + 1 cm below the costal arch. Structure, echogenicity is the norm. Gallbladder, pancreas - the norm. The spleen is 107x42 mm in size (the norm is up to 103x45 mm). There is a small amount of fluid in the pelvis. The right pleural cavity is a significant amount of fluid. Conclusion: Pleurisy on the right. Splenomegaly.

Ultrasound investigation of the abdominal cavity from 05.06.2015: there is a moderate amount of free fluid in the abdominal cavity. On the right in the pleural cavity, the fluid is free in the form of an anechoic strip 20 mm thick. There is a significant amount of free fluid in the pelvis.

Ultrasound investigation from 08.06.2015: the liver is 2 cm below the costal arch, the contour is smooth, the echostructure of the parenchyma is homogeneous, the echogenicity is increased, the vascular pattern is preserved. The gallbladder is of normal size, deformed, the walls are compacted, a hyperechoic formation is determined in the lumen, giving an acoustic hue, with a diameter of up to 30 mm (concretion). In the choledochus, a hyperechoic formation with an acoustic shadow up to 20 mm in diameter (concretion) is determined. The pancreas has smooth contours, normal size, the echostructure of the parenchyma is uniform, the echogenicity is increased. The spleen is the norm. Kidneys - the contours are smooth, clear. On the left — dimensions 104x42 mm, on the right 106x41 mm. The echostructure of the parenchyma is homogeneous. There is no free fluid in the abdominal cavity, pelvis, pleural cavities.

Consultations of specialist doctors:

Otolaryngologist from 05.26.2015: no pathology was detected.

Oculist from 29.05.2015: Complaints of periodic eye pain, headaches. The eyes are calm, the optical media are transparent. The volume of movements of the eyeballs is not limited. Fundus: the optic nerve disc is pale pink, the borders are clear, the vessels are without features.

Neurologist from 29.05.2015: Cerebrastenic syndrome of intoxication genesis.

On the third day of hospitalization (27.05.2015), the patient developed febrile fever (up to 38.50 ° C), accompanied by chills, dilute defecation, single vomiting, occasionally pain in the eyes, dark brown urine. Blood pressure increased to 135-140/75 mm Hg. By 31.05.2015, the size of the liver increased (from 1 cm below the costal arch to 3-4 cm). According to ultrasound - a large

amount of fluid in the abdominal cavity, pleural cavity and pelvis, pain in the right half of the abdomen. The patient was observed by a surgeon with suspected peritonitis, diagnostic laparoscopy was performed. Conclusion: Ascites. Indications for emergency surgery - no.

The clinical diagnosis was established: Thrombotic thrombocytopenic purpura (ICD M 31.1). Gallstone disease (K80.0)

Treatment was carried out: freshly frozen plasma 60.0 ml/kg/day for 7 days, followed by a decrease to 25.0 ml/kg/day, metopred 500 mg intravenously, drip every other day No. 3, ceftriaxone 1 gram x 2 times a day intravenously. Erythrocyte mass 250.0 No. 3, kamil 10 mg x2 times a day, enap 2.5 mg x2 times a day, lasix 20 mg with delayed diuresis. Plasmapheresis session, Acellium infusion (rituximab) 375 mg.

The girl's well-being improved dynamically: there was no fever, headaches and eye pains. Pulmonary-heart failure is satisfactory. Hemodynamics is stable. The belly is soft, painless. Liver +1.0 cm. Straw-yellow urine. There is an increase in the level of platelets, hemoglobin in the blood test. According to ultrasound data, fluid dynamics in the pleural cavities and abdominal cavity were not detected.

The diagnosis was confirmed at the Dmitry Rogachev National Medical Research Center for Pediatric Hematology, Oncology and Immunology (Moscow, Russia), where further treatment was continued. The girl is in good condition. With further follow-up for 42 months, there was no relapse of the disease.

5 Conclusion

In the foreign literature there are many works with a detailed description of the Moshkovitz syndrome mainly of adults. At the same time, there are isolated cases of the disease in childhood in the Russian literature. Identification of patients with this pathology is a serious problem for a practicing pediatrician. The article presents a clinical case of an 11-year-old child with TTP and typical clinical and laboratory symptoms of the disease. On the 3rd day of hospital stay, there was a manifestation of the classic picture of TTP with pentad: thrombocytopenia, hemolytic anemia, kidney damage, central nervous system, fever. The final diagnosis was made on the basis of a comprehensive examination in order to determine and prescribe adequate treatment. The therapy had a positive effect: body temperature was normalized, hemorrhagic and hemolytic syndromes were stopped. Despite the rarity of the disease, this clinical observation reflects the peculiarities of clinical and laboratory changes in this pathology, which will allow specialists to diagnose TTP in a timely manner and conduct adequate therapy.

At the present stage, Moshkovitz syndrome remains a fairly rare disease in children. This syndrome is a severe, difficult to diagnose pathology with an aggressive course. Without timely treatment, mortality is very high. With a quick diagnosis and early extracorporeal hemocorrection, over 80% of patients can be saved. Prevention of TTP has not been developed. In case of hereditary forms, genetic counseling is carried out. The question regarding the TPP requires additional research.

6 Availability of Data and Material

Data can be made available by contacting the corresponding author.

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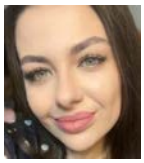

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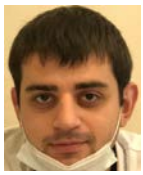

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