

Clinical Case of 11-Year-Old Child with Thrombotic Thrombocytopenic Purpura

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Abstract – Thrombotic thrombocytopenic purpura – TTP (Moschcowitz's disease) is one of the most severe forms of microangiopathy, which is characterized by intense platelet aggregation, thrombocytopenia consumption, microangiopathic hemolytic anemia, and ischemic damage to various organs. TTP is extremely rare for children and, therefore, it is difficult for clinicians to verify the disease and determine a treatment program. The disease has an aggressive course. When there is no adequate therapy, it can be fatal. The paper provides the analysis of a clinical case of an eleven-year-old girl with thrombotic thrombocytopenic purpura.

Keywords – *thrombotic thrombocytopenic purpura, Moschcowitz' disease, microangiopathic hemolytic anemia, thrombocytopenia, plasma exchange, ADAMTS-13.*

I. INTRODUCTION

Thrombotic thrombocytopenic purpura (Moschcowitz' disease) is a severe thrombotic microangiopathy, when small vessels are damaged in conjunction with hemolytic anemia, systemic platelet aggregation and intravascular coagulation, and occurs with the development of hemorrhagic syndrome, anchored by ocular pulmonary syndrome, anchored syndrome. The first paper, which described the case (by E. Moschcowitz) was published in 1925 in the journal "Archives of Internal Medicine", and in 1947 the disease was named thrombotic thrombocytopenic purpura [1, 2]. In subsequent decades, domestic and foreign

researchers studied the mechanisms of TTP development. The significant results were achieved in understanding the pathogenesis of the disease. Von Willebrand factor macromolecules (FWB), which cause uncontrolled platelet agglutination and thrombosis were the main cause of Moschcowitz' disease [3]. Further, patients with TTP had a deficiency of metalloprotease, which reduces the size of multimers of fibrobrombin factor [3]. In consequence, metalloprotease was purified and identified as ADAMTS-13. The value of this indicator <5 % is specific for TTP [4, 5]. In case with adult patients with TTP, IgG antibodies were found to inhibit the activity of this enzyme [6]. The clinical course of TTP is characterized by an acute onset: the disease develops, as a rule, suddenly, against the background of complete health, has an extremely aggressive course that requires the adequate therapy. When there is no therapy, the mortality rate can reach 100%. Often there is a flu-like prodromal period, then the disease manifests [8, 9]. The difficulties to diagnose TTP are non-specific clinical symptoms. At the same time, researchers distinguish classical pentad: 1. thrombocytopenia, 2. microangiopathic hemolytic anemia, 3. neurological disorders, 4. kidney damage, 5. fever [7–9]. However, not all five symptoms of the disease can often be found [8]. A laboratory study in the hemogram revealed the decrease in the level of platelets, erythrocytes, appearance of their fragmented forms (schizocytes), number of leukocytes is normal or slightly increased. In myelogram, erythroid and

megakaryocytic sprouts are irritated [10]. Coagulogram indices (prothrombin time and activated partial thromboplastin time – APTT) are usually normal or slightly increased. In the advanced stages, DIC may join [10, 13]. Biochemical blood tests show the increase in total bilirubin due to the indirect fraction, and increased LDH activity. The diagnosis is based on the presence of clinical and laboratory indicators. In the absence of clinically established causes of the disease, the use of primary diagnostic criteria is recommended: thrombocytopenia, microangiopathic hemolytic anemia – a diagnostic dyad [11, 12, 14]. A special diagnostic value is given to increased activity of LDH in serum [13]. Treatment of TTP has its cardinal differences from other thrombovasculitis. The reduction of microthrombus formation is achieved by using plasmapheresis with a large volume of fresh frozen plasma, antiplatelet agents, glucocorticosteroids, according to the clinical indication, red blood cell transfusion. Platelet infusions are not shown [7, 12]. Indicators of weakening of the microangiopathic process, indicative of successful TTP therapy are: the reduction of neurological symptoms, improvement of kidney function, increase in hemoglobin level, decrease in the number of reticulocytes, schizocytes, LDH concentration [8].

II. METHODS AND MATERIALS

As a clinical and laboratory presentation of thrombotic thrombocytopenic purpura with successful therapy, a description of the clinical case of a 11-year-old child in the hematology/oncology department of the RCCH was presented.

III. RESULTS

Patient R., 11 years old, was taken to hematology/oncology department of the Republican Children's Clinical Hospital on 25.05.15. She complained of general weakness, fatigue, pallor, yellow skin, hemorrhagic rashes, irritability.

The anamnesis: she was born from 2 pregnancies without pathology, 2 urgent births weighing 3400 grams.

The body develops according to her age. The girl was vaccinated by calendar.

The present disease began about three weeks before the day of hospitalization, when weakness, pallor and yellowness of the skin, hemorrhagic rashes on the lower extremities appeared. During outpatient examination in the hemogram

revealed changes in the form of a decrease in hemoglobin and platelet count, and therefore hospitalized.

When she was examined in the hospital, the condition was serious due to anemic, hemorrhagic, intoxication syndromes. A body weight is 27 kg, height is 133 cm, and level of physical development is below average. Jaundice of the skin on a pale background, pale sclera, hemorrhagic rash in the form of petechiae, ecchymosis on the lower limbs and torso. Sclera subicteric. Peripheral lymph nodes (cervical, axillary, inguinal) single, up to 0.5–1.0 cm in size, elastic consistency. Perkutorno above the lungs boxed shade of pulmonary sound, in the lower parts of the dullness. Auscultation – hard breathing, weakened in the lower parts. BH 24-26 per minute. The region of the heart is not visually altered. The boundaries of relative cardiac dullness within the age norm. The heart rate is 112–120 per minute, blood pressure is 110/65 – 140/80 mm Hg. Abdomen is soft, painless. Liver +1.0 cm, smooth edge, moderately elastic consistency. Spleen is at the edge of the costal arch. Stool is formed. Urine is light yellow (dark brown color was observed several times). Neuropsychological development is age appropriate.

Laboratory data:

Blood group B (III), Rh – positive.

Blood test from 2.06.2015: plasma metalloperoxidase activity ADAMTS-13 – 8 % of activity level in the control plasma.

Blood test for antibodies level to N factor from 4.06.2015: 23 %.

Inhibitory antibodies against ADAMTS-13 (from 03.06.2015) – positive result.

Blood test for SLE markers from 4.06.2015:

1. Lupus anticoagulant – weakly present.
2. IgG antibodies to double-stranded DNN 11,6 u/ml (0-25)
3. Antibodies to IgG phospholipids – 5,85 u/ml (0-10)
4. Antibodies to IgM phospholipids – 3,12 u/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 u/ml (0-5)
7. Antibodies to β2-glycoprotein 1 IgM – 1,26 u/ml (0-5)
8. Antibodies to IgG cardiolipin – 1,9 u/ml (0-10)
9. Antibodies to IgM cardiolipin – 1/ml (0-7)

TABLE I. HEMOGRAM VALUES

Date	Red blood cells *10 ¹²	Hemoglobin g/l	reticulocyte %	Platelets *10 ⁹ /l	White blood cells *10 ⁹ /l	Band kernels %	Eosinophils %	Segmental %	Lymphocytes %	Monocytes %	Normoblasts	ESR 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 toxicogenic granularity. Erythrocyte anisocytosis, 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
Moderate anisocytosis. Polychromatophilia. Unit schizocytes												

TABLE II. BLOOD CHEMISTRY

Date	ALT, u/l 0-40	AST, u/l, 0-37	total protein, g/l	Albumen, g/l	Total bilirubin, mk m/l	Direct bilirubin, mk m/l	K+, MM/l	Creatinine, mk m/l	Urea, mm/l	Glucose, mm/l	LDH ul, 225-450
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	-	-
9.06	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	-	-

TABLE III. GENERAL URINE ANALYSIS

Date	Colour	Transparency	Specific gravity	Protein, g/l	Leukocytes in sight	Red blood cells in sight	Cylinders in sight	Salt	Mucus	Bacteria
26.05	Light yellow	full	1018	-	0-2-1	-	-	urats	-	-
29.05	Light yellow	full	-	0.34	2-2-3	Fresh 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	Light yellow	Low level	1015	0.39	8-10-7	2-2-3	1-0-1	phosphates	++	-
02.06	Light yellow	full	1011	1.55	2-0-1	12-11-10	-	oxalates	-	-
05.06	Dark yellow	full	1020	2.840	3-3-4	5-7-7	-	oxalates. phosphates	-	-
10.06	Light yellow	full	1020	5.4	4-4-5	leached. large amounts	-	-	+	-
13.06	Light yellow	full	1010	4.6	4-5-6	15-16-14 maintained	-	urats	-	-
15.06	yellow	full	1017	3.68	1-0-1	3-4-3	-	phosphates	-	-

Coagulogram from 26.05.2015: fibrinogen – 2.73 g/l, PV – 26.8 seconds, PTI – 54.7 %, INR – 1.55

Coagulogram from 2.06.2015: PTI – 78.6 %, fibrinogen – 4.44 g/l, INR – 1.31

Coagulogram from 3.06.2015: PTI – 85.2 %, fibrinogen – 4.4 g/l, INR – 1.24

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

The bone marrow study was conducted on 05.29.2015: In the myelogram, bone marrow punctate is rich in cellular elements. Blast cells-0.8 %. Erythroid germ hyperplasia is noted. Megakaryocytic sprout narrowed. In the general examination of drugs – single megakaryocytes without pinching. Composition of granulocyte germ – no change.

Urinalysis for bile pigments of 05/29/2015: negative result.

ECG from 05/26/2015: sinus rhythm, tachycardia 120 per minute. The normal position of electrical axis. Incomplete blockade of the right branch of the bundle.

ECG from 1.06.2015: sinus rhythm, tachycardia, 125–130 per minute. The vertical position of electrical axis of the heart. Disruption of ventricular repolarization.

ECG from 4.06.2015: sinus rhythm, 110 per minute. The normal position of electrical axis of the heart. Incomplete blockade of the right branch of the bundle. There is a slight positive trend from 1.06.2015: Disruption of ventricular repolarization processes. The vertical position of electrical axis of the heart.

ECG of 06/08/2015: Sinus rhythm, 77 in 1 minute, normal position of electrical axis of the heart. Option norms.

ECHO CG from 05/27/2015: size of the walls and cavities of the heart within the age norm. Marked mitral valve prolapse – 4.2 mm (I degree). MZhP, MPP – continuous. Contractile myocardial function is satisfactory.

ECHO KG from 2.06.2015: Conclusion: there is no valve pathology. The contractile function of the myocardium is not impaired. There is no free fluid in the pericardium. Signs of intracardiac shunting was not detected.

Radiograph of the chest from 26.05.2015: pulmonary fields are transparent. The pulmonary pattern is moderately strengthened in the root zones. Shadows of roots are structural. The sinuses are free. The shadow of the mediastinum without features.

Radiograph of the chest from 2.06.2015: 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 examination of abdominal organs from 05.26.2015: liver is 1 cm below the costal arch, echostructure of the parenchyma is homogeneous, medium echogenicity, the vascular pattern is preserved. Gall bladder – N sizes, deformed, the walls are sealed, content is homogeneous. Pancreas, spleen, lobes – N.

Ultrasound examination of abdominal organs from 2.06.2015: liver +1 cm below the costal arch. Structure, echogenicity – N. Gall bladder, pancreas – N. Spleen – dimensions 107x42 mm (N up to 103x45 mm). In the pelvis insignificant amount of fluid. Right pleural cavity – a significant amount of fluid. Conclusion: Pleurisy on the right. Splenomegaly.

Ultrasound examination of abdominal organs from 5.06.2015: in the abdominal cavity there is moderate amount of free fluid. Right in the pleural cavity free fluid in the form of an anechoic strip with a thickness of 20 mm. There is a significant amount of free fluid in the pelvis.

Ultrasound examination from 8.06.2015: liver is 2 cm below the costal arch, the contour is even, the echostructure of parenchyma is homogeneous, the echo is increased, the vascular pattern is preserved. The gallbladder is of normal size, deformed, the walls are sealed, in the lumen is determined hyperechoic education, giving acoustic shade, diameter is to 30 mm (calculus). In the choledochus is determined hyperechoic education with acoustic shadow, diameter is to 20 mm (calculus). The pancreas is a smooth contour, normal size, echostructure of parenchyma is uniform, echogenicity is increased. Spleen – N. Kidneys – contours are even and clear. Left – dimensions 104x42 mm, right 106x41 mm. The echostructure of the parenchyma is homogeneous, CLA is not expanded. In the abdominal cavity, small pelvis, pleural cavities there is no free fluid.

Consultations of medical specialists:

ENT of 05.26.2015: pathology was not detected.

Optometrist from 29.05.2015: Complaints of recurrent pain in eyes, headaches. The eyes are calm, the optical media are transparent. The range of movement of the eyeballs is not limited. The fundus of the eye: optic disk, pale pink, clear boundaries, blood vessels without features.

Neurologist from 05/29/2015: Cerebrastenic syndrome of intoxication genesis.

On the third day of hospitalization (05/27/2015), the patient developed febrile fever (up to 38.50 ° C), accompanied by chills, diluted stool, single vomiting, occasionally eye pain, dark brown urine. Blood pressure rose to 135–140 / 75 mm Hg. By 31.05.2015, the size of liver increased (from 1 cm below the costal arch to 3–4 cm). Based on ultrasound examination, there is a large amount of fluid in the abdominal cavity, pleural cavity and small pelvis, pain in the right half of the abdomen. The patient was observed by a surgeon who suspected peritonitis, diagnostic laparoscopy was performed. Conclusion: Ascites. Indications for emergency surgery- no.

Clinical diagnosis established:

Thrombotic thrombocytopenic purpura (ICD M 31.1). Gallstone disease (K 80.0)

Treatment was carried out: fresh frozen plasma 60.0 ml/kg/day for 7 days, followed by a decrease to 25.0 ml/kg/day, metopred 500 mg IV/drip every other day No. 3, ceftriaxone 1 gram x 2 times iv red cell mass 250.0 No. 3, quamel 10 mg x 2 times a day, Enap 2.5 mg x 2 times a day, lasix 20 mg with diuresis delay. A plasmapheresis session, infusion of Acellium (retuksimab) 375 mg.

The girl's health condition in the dynamics improved: there was no fever, headaches, and eye pains. Pulmonary heart disease is satisfactory. Hemodynamics is stable. The abdomen 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 examination, in the dynamics of fluid in the pleural cavities and the abdominal cavity was not detected.

The diagnosis was confirmed at Dmitry Rogachev National Medical Research Center Of Pediatric Hematology, Oncology and Immunology, Moscow, where further treatment was continued. The girl in a good condition. There was no recurrence of the disease within further observation within 42 months.

IV. CONCLUSION

A. Discussion

In foreign literature there are many papers with a detailed description of TTP mainly adults. At the same time, in domestic periodicals there are isolated cases of the disease in childhood. Identification of patients with this pathology is a serious problem for practicing pediatrician. The paper presents a clinical case of 11-year-old child with TTP and typical clinical and laboratory symptoms of the disease. A feature of the clinical course of Moschowitz's disease was a long prodromal period (hospitalization 3 weeks after the onset of the disease). On the 3rd day of hospital stay, there was a manifestation of the classic TTP picture with pentad: thrombocytopenia, hemolytic anemia, kidney damage, central nervous system, fever. The final diagnosis was made through a comprehensive examination to define and prescribe adequate treatment. The therapy (infusion of frozen plasma, erythrocyte mass, metipred, further prednisone, ceftriaxone, plasmapheresis, infusion of acerbia, etc.) gave a positive effect: body temperature normalized, hemorrhagic and hemolytic syndromes were stopped. Despite the rarity of the disease, the present clinical observation reflects the characteristics of clinical and laboratory changes in this pathology, which will enable specialists to diagnose TTP in a timely manner and apply adequate therapy.

B. Conclusion

At the present stage, thrombotic thrombocytopenic purpura (Moschowitz' disease) remains a rather rare disease for

children. Lack of specialists' awareness affects the timing of diagnosis and timeliness of adequate therapy. The availability of up-to-date information in domestic publications on this nosology for practitioners in public health will help to increase the awareness and improve the quality of care for patients with TTP.

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