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Multisystem inflammatory syndrome complicated by pulmonary embolism in a child

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Purpose — to present a clinical case of a particular complication of post-COVID multisystem inflammatory syndrome (MIS) — pulmonary embolism (PE) which developed due to primary hereditary thrombophilia in a child for better understanding of the MIS evolution and prognosis in children (MIS-C).

Case report. In an 11-year-old boy who previously had no hemorrhagic manifestations, the first symptoms of the disease occurred in the form of fever and a hemorrhagic rash on the lower extremities. Later, he developed signs of respiratory failure, his condition worsened, and bilateral community-acquired viral pneumonia caused by COVID-19 was diagnosed. The child presented with post-COVID MIS manifested as PE, which caused further genetic examinations for hereditary thrombophilia. Primary thrombophilia was detected (F2 gene — prothrombin (20210 G>A) D68.5). Concomitant hereditary pathology was probably the reason for a severe course of the infection and the development of a complication in the form of PE requiring intensive and long-term anticoagulant therapy.

Conclusions. In case of PE detection, especially in young patients, examinations to confirm or rule out hereditary or acquired thrombophilia are required, that defines recurrent venous thromboembolism prevention programs. This clinical case report is a contribution to the study on the issues of MIS-C, defining links between pulmonary complications (transient or persistent) and serious sequelae in the future.

The research was carried out in accordance with the principles of the Helsinki Declaration. The informed consent of the patient was obtained for conducting the studies.

No conflict of interests was declared by the authors.

Keywords: multisystem inflammatory syndrome, children, pulmonary embolism, primary thrombophilia, anticoagulant therapy.

Мультисистемний запальний синдром у дитини, ускладнений тромбоемболією легеневої артерії

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Під час виникнення пандемії COVID-19 у дітей спостерігалися часті ускладнення у вигляді постковідного мультисистемного запального синдрому (MIS). Для кращого розуміння еволюції та прогнозу MIS у дітей (MIS-C) заслуговує уваги описаний нами особливий вид ускладнення — тромбоемболія легеневої артерії (ТЕЛА), що розвинулася на тлі первинної спадкової тромбофілії в дитини.

Мета — описати клінічний випадок особливого ускладнення MIS — ТЕЛА, що розвинулася на тлі первинної спадкової тромбофілії в дитини.

Клінічний випадок. У хлопчика віком 11 років, у якого раніше не було геморагічних проявів, перші симптоми захворювання виникли у вигляді лихоманки і геморагічної висипки на нижніх кінцівках. Пізніше з'явились ознаки дихальної недостатності, стан дитини погіршився, була діагностована позалікарняна двобічна вірусна пневмонія, викликана COVID-19. У дитини розвинувся постковідний MIS у вигляді ТЕЛА, що зумовило подальше генетичне обстеження на спадкову тромбофілію. Виявлена первинна тромбофілія (Ген F2 — протромбін (20210 G>A) D68,5). Наявність спадкової патології, скоріше за все, спричинила тяжкий перебіг інфекції та розвитку ускладнення у вигляді ТЕЛА і потребувала проведення інтенсивної й тривалої антикоагулянтної терапії.

Висновки. У разі виявлення ТЕЛА, особливо в пацієнтів молодого віку, обстеження з метою підтвердження/виключення вродженої або набутої тромбофілії є обов'язковим та визначає програму профілактики повторних венозних тромбоемболій. Опис клінічного випадку є внеском у вивчення проблеми MIS-C, встановлення зв'язку легеневих ускладнень (транзиторних або стійких) із серйозними наслідками в майбутньому.

Дослідження виконано відповідно до принципів Гельсінської декларації. На проведення досліджень отримано інформовану згоду батьків дитини.

Автори заявляють про відсутність конфлікту інтересів.

Ключові слова: мультисистемний запальний синдром, діти, тромбоемболія легеневої артерії, спадкова тромбофілія, антикоагулянтна терапія.

Introduction

One of the major challenges facing modern medicine all over the world in 2019–2022 was the COVID-19 pandemic. Published information concerning the course, treatment, and presence of complications in children during that time was rather controversial [8,23]. Pediatric COVID-19 cases demonstrated specific characteristics [6,11], a novel pediatric disease — multisystem inflammatory syndrome in children (MIS-C) was termed and thought to be associated with COVID-19 infection [12,19]. According to the Centers for Disease Control and Prevention published findings in May 2020, an incidence of MIS-C was estimated to be only 600 cases of MIS-C in the United States, and there were already about 2060 incidents in February 2021 [10]. The criteria for a diagnosis of MIS-C (based on the Interim Guidance, 2020) include the presence of six signs: clinically severe disease requiring hospitalization, age <21 years, fever >38°C lasting >24 hours, laboratory evidence of inflammation >1 parameter, mul-

tisystem organ involvement (two organs or systems) and positive laboratory testing for current or recent COVID-19 infection (positive Polymerase chain reaction (PCR) test, detection of antigen, presence of antibodies or COVID-19 exposure within a previous month before the symptom onset) [21]. As the pandemic progressed, there were reports of increased rates of venous and arterial thrombotic events in children with COVID-19 and MIS-C. In accordance with the published data, thrombosis was observed in up to 27% of cases in children with MIS [7].

Besides, over the recent decades, the incidence of venous thromboembolism (VTE) has significantly increased in children, but most importantly, across all age groups [3]. As per results of analysis, 12.4% of VTE caused the development of post-thrombotic syndrome, 8.1% — frequently recurring thrombosis [5,14]. VTE diagnosis, especially in young patients, may be associated with inherited or acquired thrombophilia — a hereditary or acquired condition characterized by an increased tendency of blood to clot in vessels with the occurrence of VTE — deep vein thrombosis (DVT) and pulmonary embolism (PE) [24].

More epidemiological and clinical studies need to be done in order to better understand the evolution and prognosis of MIS-C, as well as to define therapeutic strategies [20,23].

The ***purpose*** of the study — to present a clinical case of a particular complication of post-COVID MIS — PE which developed due to primary hereditary thrombophilia in a child.

Clinical case

Informed consent of the child's parents was obtained for the research. We have analyzed the clinical case of an 11-year-old *boy Ya.*, who was examined and treated at the ME «Regional Medical Center of Family Health (RMCFH)» of Dnipropetrovsk Regional Council» with a clinical diagnosis: post-COVID MIS-C (PE, bilateral community-acquired viral pneumonia), primary thrombophilia (F2 gene — prothrombin (20210 G>A) D68.5), secondary metabolic cardiomyopathy.

Results

The patient presented to the hospital with complaints of weakness, drowsiness, difficulty breathing, shortness of breath at rest, cough, and bruises on his arms and legs.

Based on a clinical history, the disease onset was acute, when parents first noticed a hematoma in the upper third of the left thigh in their previously completely well-being child two weeks before a hospitalization. A week after that, the child also developed hematomas on the skin in the projection of the ankle joints, on the shins and upper extremities, the occurrence of which was accompanied by an increase in body temperature up to febrile values, moderate shortness of breath, swelling of the lips. The boy was treated by a family doctor with a diagnosis of acute respiratory disease and received symptomatic treatment. The child was admitted to the city hospital as his condition clinically deteriorated (worsening of respiratory disorders). After a general clinical examination, chest X-ray and ultrasound examinations, a presumptive diagnosis was made: left-sided pneumonia. A PCR test was negative for SARS-CoV-2, but a medical history of contact with his father who had coronavirus disease a week before the onset of the first symptoms in the child was positive. IgG and IgM antibodies against COVID-19 were afterwards detected in the boy at a hospital. The child was diagnosed with bilateral polysegmental pneumonia, PE and referred for further examination and treatment to the RMCFH.

Upon admission to the RMCFH, the child's condition was serious due to signs of degree II respiratory failure. On examination: shortness of breath at rest, persistent dyspnea with pronounced involvement of accessory muscles in the act of breathing, subcostal, intercostal, supracostal retractions. The level of consciousness was not impaired, signs of meningeal irritation were negative, no focal neurological symptoms were detected. The skin was pale pink in color, moist, body temperature — 37°C, respiratory rate — 33/min, heart rate — 90 bpm, blood pressure of 140/65 mmHg corresponded to grade II hypertension. When breathing atmospheric air, oxygen desaturation up to 88–90% was detected. Auscultation revealed rough respiratory sounds over the lungs, heard symmetrically, there were no rales; heart sounds were rhythmic, muffled. The abdomen was soft, nontender to deep palpation; the liver was enlarged by one cm in the right midclavicular line; the spleen was not enlarged. Defecation and urination were independent, urine was light, diuresis was adequate.

The dynamic laboratory examination findings of the boy are presented in tables 1–3.

Admission laboratory examinations including clinical blood tests revealed neutrophilic

Table 1

Dynamics of clinical blood test parameters

Parameter	Reference values	Day of hospital stay				
		Day 1	Day 7	Day 13	Day 20	Day 23
Erythrocytes, T/L	3.5–4.7	4.00	3.50	3.7	4.03	4.50
Hemoglobin, g/L	110–145	125	**99**	110	117	132
Platelets, G/L	150–410	**65**	**78**	**48**	169	**140**
Leukocytes, G/L	4.5–10.5	**15.0**	**12.6**	14.9	10.0	8.9
Myelocytes, %	0–1	0	0	0	0	0
Metamyelocytes, %	0–1	0	0	0	0	0
Band neutrophils, %	1–5	**17**	**15**	**8**	4	2
Segmented neutrophils, %	35–65	**68**	**76**	41	50	60
Lymphocytes, %	20–54	**3**	**4**	36	25	30
Monocytes, %	2–10	5	5	9	10	7
Eosinophils, %	1–5	**7**	**10**	**6**	10	1
Basophils, %	0–1	0	0	0	1	0
ESR, mm/h	4–12	**20**	**20**	**18**	9	6

Note: ESR — Erythrocyte Sedimentation Rate.

Table 2

Dynamics of coagulogram parameters

Parameter	Reference values	Day of hospital stay				
		Day 1	Day 7	Day 13	Day 17	Day 23
INR, c.u.	0.8–1.2	1.0	1.2	1.2	1.12	1.13
Quick prothrombin, index / %	70–100	95	79	83	89	83
Thrombin time, s	15–21	13.7	16.4	15.6	14.6	19
APTT, s	25–43	24,4	31,4	24,3	25	33
Fibrinogen, g/L	2–4	6.2	2.9	3.9	4.9	4.3
FFMC, mg/%	3–4	3.0	4.0	3.0	4.0	5.0
D-dimer, μg/mL	0.5		2.19		2.21	

Notes: INR — International Normalized Ratio; APTT — Activated Partial Thromboplastin Time; FFMC — Fibrinogen-Fibrin Monomer Complexes.

leukocytosis with a leukocyte formula left shift, thrombocytopenia, and an increase in erythrocyte sedimentation rate (ESR). Biochemical blood analysis showed hypoproteinemia, hypoalbuminemia, increased lactate dehydrogenase (LDH) and C-reactive protein (CRP). The coagulogram indicated hemostasis disorders in the form of disseminated intravascular hypercoagulation characteristics and an increase in D-dimer. Natriuretic peptide was within the normal range (3.94 pc/ml) being additionally tested. A clinical urinalysis revealed slight proteinuria, moderate leukocyturia and microerythrocyturia. These changes were transient and eliminated within a week. The rate of diuresis was sufficient — 1.8 ml/kg/h.

Instrumental examinations demonstrated signs of left ventricular overload through an assessment of ECG; hypertrophy of the interventricular septum (IVST — 9 mm), an increase in the right ventricle chamber dimension (RVD — 18 mm) and pulmonary artery blood flow velocity (PABFV — 34 m/s) with normal myocardial contractility (ejection fraction — 67%) determined via Echo-CG.

Contrast-enhanced computed tomography angiography of the chest and mediastinum organs revealed the presence of bilateral areas with increased attenuation of the lung tissue as a ground-glass opacity pattern localized mainly on the right as well as bilateral pulmonary consolidations which were triangular in shape in the lower lobes (S8) distributed peripheral to subpleural spaces. There were no bronchial or tracheal obstructions. After a contrast agent injection into the right and left pulmonary arteries, multiple filling defects of different sizes were seen up to the level of the segmental pulmonary arteries. Conclusions: PE, bilateral pulmonary infarction-associated pneumonia in the lower lobes, bilateral polysegmental pneumonia.

A lung ultrasound examination revealed right-sided pneumonia (a hypoechoic consolidated area of lung tissue was visualized) and signs of right-sided pleurisy (about 100 ml of pleural effusion was detected).

An abdominal ultrasound examination showed hepatomegaly (right lobe — 110 mm, left lobe — 60 mm) and enlargement of the pancreas (head/body/tail — 15/13/16 mm).

Doppler ultrasound scanning of the renal arteries revealed that the blood flow velocity parameters corresponded to the norm (V min-max in the right main renal artery — 0.24–0.74; V min-max

Table 3

Dynamics of blood biochemical parameters

Parameter	Reference values	Day of hospital stay				
		Day 1	Day 5	Day 10	Day 15	Day 20
ALT, units/L	<39	28	35	59	–	90
AST, units/L	<47	24	22	33	–	38
Alkaline phosphatase, units/L	145–420		100		–	
Total bilirubin, μmol/L	3.4–21.5		9	14,8	–	7
LDH, unit/L	<295		427	360		
Total protein, g/L	52–78	59	74	58	58	65
Albumin, g/L	35–54	30	40	31	29	35
Urea, mmol/L	1.8–6.4	5.9	4.0	5.2	4.3	2.1
Creatinine, μmol/L	45–105		56			61
Glucose, mmol/L	3.8–6.1		5.1			5.0
Amylase, U/L	<120	73	49	65	–	47
CPK, U/L	<145		44			
Urea nitrogen, mmol/L	1.2–3.9	2.7	1.9	2.5	–	1.0
C-reactive protein, mg/mL	<6	12	6	6	6	6
Na+, mmol/L	135–148	138	142	140	141	143
K+, mmol/l	3.5–5.3	4.3	4.3	4.4	3.9	4.4
Cl-, mmol/l	98–107	109	115	114	112	112

Notes: ALT – Alanine Aminotransferease; AST – Aspartate Aminotransferase; LDH – Lactate Dehydrogenase; CPK – Creatine Phosphokinase.

in the left main renal artery — 0.23–0.73), and spectral parameters were increased (Resistive Index of the right main renal artery — 0.68; Resistive Index of the left main renal artery — 0.70).

The diagnosis of MIS was made on the basis of the following criteria: severe disease requiring hospitalization, age <21 years, fever >38°C that lasted longer than 24 hours, laboratory signs of inflammation >1, multisystem organ involvement (respiratory, cardiovascular systems and skin) as well as confirmed COVID-19 (the history of close contact with the known case of COVID-19 within the previous month and the presence of detected antibodies). The following laboratory signs of inflammation were evidence of MIS-syndrome: increased CRP, ESR, fibrinogen, D-dimer, LDH along with neutrophilic leukocytosis, decreased albumin level, and thrombocytopenia.

The diagnosis of subtotal PE was made based on the chest CT and a cardiac surgeon consultation.

The diagnosis of hereditary thrombophilia was confirmed by using genetic markers of thrombophilia panel. A genetic examination revealed primary thrombophilia for the first time in the child's life: Gene F2 — prothrombin (20210 G>A); Gene F7 — (10976G>A); F13A1(103G>T); PAI -1 (675 5G>4G) ITGB3-b — integrin (1565 T>C) — mutation, heterozygous state was detected. His brother carried the same mutation, that was not accompanied by cardiovascular complications.

During his stay in the hospital, the boy's temperature periodically rose to febrile values, a hemorrhagic maculo-petechial rash occurred over the trunk and neck followed by itching. He was also developed cough, a mixed type of breathlessness at rest and worsening dyspnea on exertion. Arterial hypertension was documented only on admission and did not require antihypertensive therapy. The boy underwent detoxification therapy, oxygen therapy, antithrombotic and antibacterial treatment.

Schönlein–Henoch purpura and hereditary thrombophilia were considered as a differential diagnosis in the patient presenting with a hemorrhagic syndrome of the bruise-like type. Other systemic diseases were also ruled out: antiphospholipid syndrome, systemic vasculitis. The child was consulted by professors at the Departments of Pediatrics and Infectious Diseases, a cardiac surgeon, a cardiorheumatologist, a hematologist, as well as by the Head of the Hemostasis Department at OHMATDYT hospital in Lviv.

Given the concurrent course of MIS with thrombophilia, it was decided to escalate low-molecular-weight heparin (enoxaparin) therapy to requiring additional direct-acting oral anticoagulant (rivaroxaban) at a dose of 5 mg/day, to continue dynamic monitoring of the child's condition, to control D-dimer, ferritin, CRP, procalcitonin, coagulogram parameters.

The child received treatment according to Protocol No. 3094 «Provision of medical assistance for the treatment of coronavirus disease (COVID-19)» dated December 31, 2020 [18] and International

Recommendations «Interim Clinical Guidance for adults with suspected or confirmed COVID-19», Belgium, December 1, 2020 [15,21], namely, detoxification therapy, glucocorticoids, and syndromic therapy. He received fraxiparin, enoxaparin and rivaroxaban for the purpose of antithrombotic treatment. From the first day of his stay at the RMCFH, the patient was prescribed dexamethasone at a dose of 0.1 mg/kg body weight, which amounted to 6 mg/day (2 mg 3 times a day), for 10 days with gradual withdrawal. Fraxiparin was administrated at a dose of 0.1 ml/10 kg body weight (5700 IU anti-Xa) once daily subcutaneously for one week, and then — enoxaparin 0.5 ml 2 times a day (10,000 anti-Xa IU, 200 anti-Xa IU/kg) for 8 days with the following switch to rivaroxaban first for 4 days at a dose of 2.5 mg 2 times (5 mg/day), and then for 3 months with an increased dose to 15 mg/day.

The patient presented improvements in his general condition as well as normalized laboratory findings and was discharged home after a 25-day stay at the hospital with instructions for further follow-up by a family doctor and a cardiologist. It was recommended to control motor (with gradual expansion) and drinking regimens, to maintain treatment with rivaroxaban at a dose of 15 mg/day for 21 days with a possible further extension of up to three months with the dose correction. The patient was advised to check-up blood parameters and coagulogram with glomerular filtration rate calculation once every two weeks and Echo-CG and ECG — after three weeks.

Discussion

The presented clinical case demonstrates the development of a particular complication of post-COVID MIS in the child — PE. PE is a condition characterized by an obstruction of the pulmonary artery or its main branches with a clot or its fragments which are formed in the systemic circulation veins or the right heart cavities and subsequently displaced to the pulmonary circulation with the blood flow [17].

It is necessary to rule out thrombophilia (a predisposition to thrombi formation with a localization in vessels or heart cavity) in patients diagnosed with PE. According to the British Society for Haematology (BSH) Clinical Guidelines, thrombophilias are inherited or acquired conditions that are associated with VTE, such as DVT and PE [2]. Thrombophilia does not always result in thrombosis, but significantly increases the risk of its occurrence, that is, so, it is a pathological condition that leads to thromboembolism. The frequency of hereditary thrombophilias predisposing to VTE is 5–10% in the general population and reaches 40% in patients who have had a VTE [5]. The most common hereditary thrombophilias include the carriage of Leiden mutations, prothrombin mutations, protein C deficiency, protein S deficiency, and antithrombin deficiency [25]. According to Hedegaard S.S. et al., 9 of the 27 (33%) children with venous thrombosis had hereditary or acquired thrombophilia, which was significantly higher than in the general population [13].

Being comprehensively assessed, the examined child was diagnosed with an underlying hereditary disease — primary thrombophilia (prothrombin mutation), that caused the development of SARS-CoV-2 thrombotic complications. A mutation at nucleotide 20210 in the gene encoding prothrombin results in states with increased circulating concentrations of prothrombin, which is further proteolytically converted to thrombin. According to studies by F. Vazquez et al., the prevalence of this gene mutation 20210 was from 2 to 5% in the general population, and more often among white patients [25].

The pathogenesis of thrombosis almost invariably is complex, and thrombotic episodes occur as a result of a combined influence of inherited genetic and environmental factors. There is currently little information available about the cause of thrombosis in MIS-C, although the mechanism is thought to be similar to that in acute COVID-19. It is believed that the main triggering factor of hypercoagulation in SARS-CoV-2 infection is direct or indirect damage to the endothelium as a result of viral infection and systemic inflammation, resulting in the activation of tissue factor pathways, platelets, and several cytokines [7].

The coagulopathy that occurred in the patient, whose case is presented in this article, was related to COVID-19 and had its own mechanistic characteristics. The presence of mutations in the genes encoding central regulators of thrombopoiesis (i.e., thrombopoietin and its receptor c-MPL or the receptor's effector kinase) perhaps intensified the prothrombotic state, ultimately leading to the development of pulmonary thromboembolism associated with certain risk factors [4]. According to V. Wanga et al., children with a history of concomitant diseases (most often — obesity — 32.4% and bronchial asthma or reactive airways disease — 16%, respectively) were more likely to develop a severe course of the disease and

had a higher risk of death from COVID-19 [26]. Acute diseases or concomitant diseases are probably associated with an increased risk of thromboembolic diseases in children.

The majority of patients with MIS had a relevant history of previous exposure to someone infected with SARS-CoV-2 or tested positive by serological tests or RT-PCR. Based on the epidemiological data, M. Santaniello at al. have noticed that SARS-CoV-2 infection acted as a trigger for the post-infectious inflammatory process [20].

According to a systematic literature review conducted by H. Singh et al., cutaneous manifestations of MIS-C in children were quite common (25%), occurred diversely and had significant implications for early diagnosis of the disease [22]. Skin lesions in our patient had the character of the hemorrhagic maculo-petechial rash occurred over the trunk and neck, which was accompanied by itching. The manifestation of cutaneous symptoms could also be explained by the high serum prothrombin level in the child diagnosed with hereditary thrombophilia.

The inflammatory process in coronavirus disease is the major precipitating factor for coagulopathy, however, the precise mechanisms linking inflammation with hemostasis dysregulation and thrombosis warrants further long-term studies. Research data have suggested a significant elevation of laboratory inflammatory markers such as CRP, ferritin, procalcitonin, D-dimer, and natriuretic peptide in children with MIS after confirmed COVID-19 infection. Severe viral infections activate the blood coagulation system and increase the risk for thromboembolism. A viral infection is responsible for the activation of endothelial cells, platelets and leukocytes, followed by the formation and release of thrombogenic microparticles containing tissue factor, which further drives the cascade of coagulation [1,9,12,16]. Increased levels of CRP to 12 mg/ml, LDH to 427 units/l, and D-dimer to 2.21 μg were detected in the examined boy, indicating the presence of inflammatory signs, that could have caused coagulation disorders in the child.

Conclusions

Multisystem inflammatory syndrome in children associated with the coronavirus disease 2019 has a wide range of clinical manifestations and requires timely diagnosis, adequate treatment and careful dynamic monitoring.

On the one hand, the inflammatory process in the coronavirus disease is the major trigger of coagulopathy, on the other hand, the presence of the underlying condition in the form of hereditary thrombophilia in the child complicated the course of multisystem inflammatory syndrome and contributed to the development of pulmonary embolism.

In case of pulmonary embolism detection, especially in young patients, examinations to confirm or rule out hereditary or acquired thrombophilia are required, that defines recurrent venous thromboembolism prevention programs.

This clinical case report is a contribution to the study on the issues of multisystem inflammatory syndrome in children, defining links between pulmonary complications (transient or persistent) and serious sequelae in the future.

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