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A Case of Pediatric Multisystem Inflammatory Syndrome Temporally Associated with SARS-CoV-2

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Introducion. COVID-19 in children is a relatively mild disease. Though a more serious condition characterized by systemic inflammation does occur in children in a Kawasaki disease-like form named multisystem inflammatory syndrome (MIS-C). MIS-C in children is a less common pathology.

Case Report. A clinical case of multisystem inflammatory syndrome in children (MIS-C) temporally associated with SARS-CoV-2 infection in a previously healthy preschool-age girl is presented. The disease had an incomplete Kawasaki disease-like form corresponding to this syndrome in children and adolescents as defined by WHO and CDC criteria.

Conclusion. This clinical case draws the attention of general practitioners and pediatricians to the peculiarities of this type of syndrome diagnosis and management.

Keywords: COVID-19; PEDIATRIC MULTISYSTEM INFLAMMATORY SYNDROME, COVID-19 RELATED; CHILD

INTRODUCTION

The outbreak of COVID-19 in late December 2019 has brought significant challenges worldwide. WHO data for September 2021 shows that COVID-19 affected almost 224.2 million people and caused more than 4.6 million deaths (1). According to the Center of Public Health, 2.3 million cases and 54.6 thousand deaths were recorded in Ukraine as of September 2021 (2).

COVID-19 in children is a relatively mild disease. However, a more serious condition characterised by systemic inflammation in children and concurrent COVID-19 was published in the United States on 7 April 2020 (3). The disease was named Paediatric inflammatory multisystem syndrome and is temporally associated with the SARS-CoV-2 infection (PIMS-TS). Later, similar cases were encountered worldwide and named Multisystem inflammatory syndrome in children (MIS-C) temporally associated with the SARS-CoV-2 infection (4).

Seven cases of MIS-C were reported in the Ternopil region of Ukraine in the autumn-spring period of 2020-2021 (5). This paper presents one such case for improving timely diagnosing and adequate management of such patients.

CASE REPORT

A girl aged four years and eleven months was hospitalized at the Paediatric Intensive Care Unit (PICU) in the Ternopil City Children's Municipal Hospital on day six of her disease, with a fever of 39.0°C, rhinorrhea, cough, abdominal pain, vomiting, diarrhea, lethargy, and rash. The disease had started with rhinitis and coughing. Two days later, a poorly controlled fever developed. Abdominal pain and vomiting occurred on day five, and a rash was noticed on the morning of day six. The patient's allergic and family history was favourable.

Upon admission, the general condition was severe, with the patient conscious but sleepy. The vital signs were as follows:

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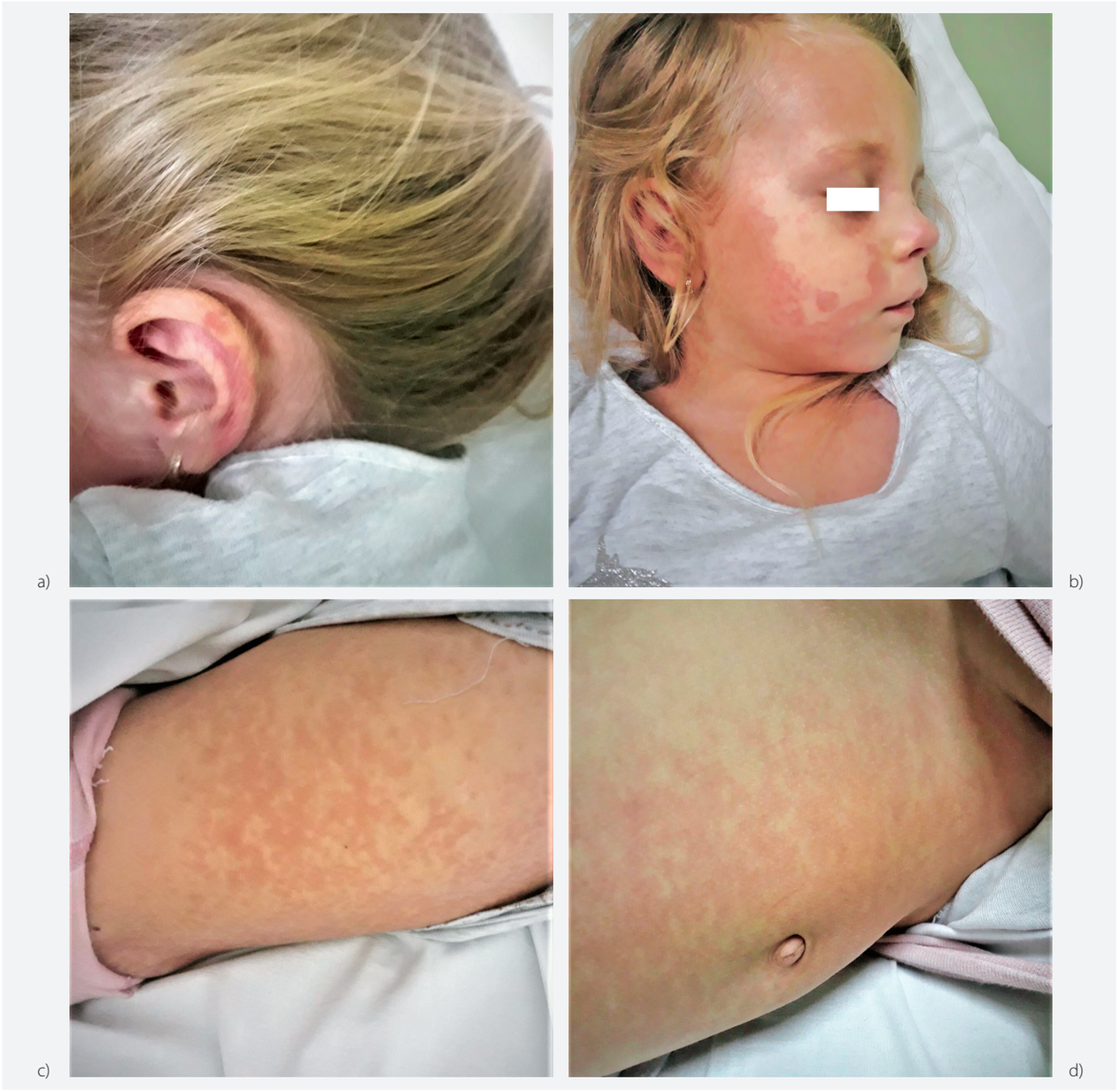

FIGURE1.**a-d. Exanthema in the patient on the day of admission.**

38.5 °C, HR 136 b.p.m, RR 26 b.p.m, BP 88/46 mm/Hg, oxygen saturation 96%, and capillary refill time 2 sec. The girl's skin was pale with an abundant macular-erythematous rash on the trunk, face, ears, and neck (Figure 1.a-d). Also present was edema of the eyelids with nonexudative conjunctivitis. The lips were dry and red. The oral mucosa was hyperemic and tongue coated. Peripheral lymph nodes were not enlarged, but soft and painless. Relative heart borders were normal, with heart sounds rhythmic, loud and clear. Breathing was vesicular. The abdomen was soft and painless, with the liver +3 cm and a tip of the spleen below the rib arch. Meningeal signs were negative.

The blood test revealed anemia, leukocytosis with a left shift, lymphopenia, and increased ESR (Table 1). Urinalysis showed hyperstenuria and ketonuria. Blood chemistry showed elevated liver enzymes, hypoalbuminemia, increased urea, triglycerides and inflammatory markers (C-reactive protein, procalcitonin), hypokalemia, hypomagnesemia and iron deficiency. The coagulogram demonstrated disseminated intravascular coagulation (Table 2).

Reverse transcriptase-polymerase chain reaction (RT-PCR) results of throat and nose smears for SARS-CoV-2 both in the child and her mother were negative. The enzyme-linked immunosorbent assay (ELISA) showed negative specific

TABLE 1. Dynamics of clinical blood count

Laboratory values	Reference values	Date								
		06.11	07.11	08.11	09.11	11.11	12.11	13.11	16.11	19.11
Red blood cells	3.80-5.80 M/ul	3.82	*3.65*	*3.30*	*3.50*	*3.24*	*3.13*	*3.17*	*3.04*	*3.38*
Hemoglobin	120-140 g/l	*114*	*100*	*89*	*104*	*95*	*92*	*95*	*92*	*105*
Hematocrit	36-44	33	31	28	30	28	27	28	27	32
Platelets	200-400 K/ul	*63*	*151*	*142*	*113*	322	**449**	**564**	**748**	**869**
White blood cells	3.5-10.0 K/ul	**17.19**	**11.5**	**10.2**	**14.68**	**33.29**	**42.14**	**40.03**	**13.70**	7.78
Myelocytes	0 %	1	-	-	**6**	-	**2**	**6**	**5**	-
Juvenile neutrophils	0-1 %	**13**	-	-	**1**	-	**8**	**3**	-	-
Band neutrophils	1-5 %	**48**	**28**	**28**	**21**	**17**	**15**	**11**	**6**	5
Segmented neutrophils	35-65 %	28	63	56	64	69	53	46	43	36
Lymphocytes	20-54 %	*6*	*7*	*12*	*7*	*10*	20	*15*	36	50
Monocytes	2-10 %	2	2	4	1	3	1	13	5	6
Eosinophils	1-5 %	2	0	0	0	1	1	6	5	1
Erythrocyte Sedimentation Rate	4-12 mm/hr	**40**	**52**	**62**	**46**	**34**	**25**	**47**	**57**	**45**
Toxic granulation of neutrophils	-		+++	+++	+++					

IgM and positive specific IgG (6.13 g/l). An abdominal ultrasound revealed hepatomegaly (right lobe transverse diameter - 101 mm), splenomegaly (86x38 mm) and increased echogenicity of the liver and cortex of the kidneys. Ultrasound dynamics were negative, including increased hepatomegaly (114 mm); the appearance of gallbladder edema and ascites (presence of fluid in the small pelvis 12-13.5 mm with 18.5 mm in the liver angle and 6.5 mm in the spleen angle) on day 12 of the illness. A gradual decrease in pathological symptoms was noticed four days later. The ECG and echocardiography on admission and in the course of the condition did not show any pathological changes in the heart, coronary arteries, or signs of pulmonary hypertension. The chest radiogram was normal. CSF investigation, head and neck MRI did not detect any pathology. Throat, blood, and urine cultures were negative for pathogenic streptococci and staphylococci.

The data on the patient's present history showed hyperthermia for more than three days and multisystem involvement, i.e., dermatologic (skin and mucosal), gastrointestinal (vomiting, abdominal pain, elevated liver enzymes), cardiovascular (hypotension) symptoms, coagulopathy, including elevated markers of inflammation and positive specific IgG to SARS-CoV-2 test led to the diagnosis of Kawasaki disease-like incomplete MIS-C based on the WHO and CDC criteria of this syndrome in children and adolescents (6, 7).

The patient's treatment corresponded to a national consensus management pathway for MIS-C (8). It was started on the day of admission with intravenous immunoglobulin (IVIG) 2 g/kg and moderate doses of parenteral dexamethasone (2.5 mg/kg/day by prednisolone BID). On the third day, the dose of dexamethasone was increased to 5 mg/kg/day for two days (due to prolongation of fever and negative abdominal ultrasound dynamics) and discontinued three days later with a previous lowering of the dose (3.3-1.7-0.8 mg/kg/day) as the patient had a considerable clinical improvement and no signs of affection of the heart and coronary arteries. Biological therapy was not administered, as the child improved on IVIG and dexamethasone. No antiviral treatment was given (due to the negative RT-PCR test). Broad-spectrum antibiotics were administered, i.e., ceftriaxone 100 mg/kg/day BID and meropenem 125 mg/kg/day TID for 10 days. Antiplatelet and anticoagulation therapy with low doses of acetylsalicylic acid (4 mg/kg/day) and heparin (250 IU every 6 hours for 6 days) were started since hospital admission. The rest of the treatment consisted of adequate hydration.

The course of the disease was positive. The patient was transferred to the infectious department after ten days. Five days later, the girl was discharged home exhibiting clinical improvement (temperature normalizing, toxic, abdominal, skin, and mucosal symptoms disappearing) along with completely normal laboratory and instrumental test results. She was recommended acetylsalicylic acid 4 mg/kg/day for three months, with a recommended blood test every fortnight and regular electrocardiography and echocardioscopy once a month for three months to monitor heart and coronary arteries. To date, all indicators of the child's health remain normal.

DISCUSSION

MIS-C is an autoinflammatory disorder resulting in inflammation of multiple organ systems. The cause of MIS-C is unknown

TABLE 2. Dynamics of biochemical blood analysis

Laboratory values	Reference values	Date				
		06.11	09.11	11.11	16.11	19.11
Alanine aminotransferase	<45 U/L	**99**	12	40	**63**	**44**
Aspartate aminotransferase	<35 U/L	**58**	28	**55**	**51**	**51**
Alkaline phosphatase	42-383 U/L	368	193	142	**465**	244
Total bilirubin	3.4-21.5 µmol/L	18.1	8.1	7.9	5.5	6.4
Direct bilirubin	0.86-5.4 µmol/L	**13.1**	4.5	3.3	2.5	2.3
Lactate dehydrogenase	<480 U/L	**489**	207	218	339	-
Gamma-glutamyl transferase	<55 U/L	**63**	24	38	47	40
Total protein	55-83 g/L	**45**	78	66	74	85
Albumin	35-54 g/L	**29.1**	**28.3**	**26**	**33.1**	-
Urea	1.7-7.3 mmol/L	**8.38**	4.61	5.76	4.08	4.87
Creatinine	27-98 µmol/L	58	49	31	31	36
Glucose	4.1-6.1 mmol/L	4.44	**7.17**	**7.7**	4.7	5.01
Amylase	<100 U/L	31	44	75	**123**	-
Lypase	8-78 U/L	23	46	-	-	-
Triglycerides	0.34-1.13 mmol/L	**5.97**	**2.45**	**1.43**	1.10	-
Creatine phosphokinase	<247 U/L	45.7	56.8	-	-	-
Uric acid	208-428 µmol/L	268	164	93	-	-
Troponin 1	< 0.16 ng/ml	-	**0.16**	-	0.124	-
C-reactive protein	< 5 mg/L	**12.8**	-	**10.1**	3.7	0.5
Procalcitonin	< 0.10 ng/ml	**5.7**	**5.6**	**0.5**	**0.4**	-
Ferritin	22-350 ng/ml	23.38	30.3	-	18.66	-
Anti-Streptolysine O	<200 U/ml	136		-	200	
Sodium	135-148 mmol/L	-	134.7	136.9	139.2	-
Potassium	3.5-5.1 mmol/L	-	*2.81*	4.68	3.64	-
Chlorides	96-111 mmol/L	-	98.0	91.0	100.9	-
Calcium	2.2-2.7 mmol/L	*2.08*	*1.05*	*2.13*	*2.10*	-
Magnesium	0.68-1.07 mmol/L	0.84	0.90	*0.91*	*0.55*	-
Phosphorus	1.45-1.78 mmol/L	1.79	*1.16*	*0.91*	*1.22*	-
Iron	8.95-21.48 mmol/L	*8.9*	*6.5*	11.9	**27.8**	-
Prothrombin time	10-15 s.	13.7	*15.7*	12.3	13.5	-
Prothrombin index	70-100 %	90.4	*67.5*	**116.4**	92.6	-
Thrombin clotting time	15-21 s.	20.7	19.0	**22.8**	**22.5**	-
Activated partial thromboplastin time	25-43 s.	41.1	*29.9*	27.1	33.9	-
Fibrinogen	2-4 g/L	**4.78**	*1.87*	*1.27*	2.61	-
International Normalized Ratio	0.9-1.3	1.05	1.24	0.93	1.04	-
D-dimer	< 250 ng/ml	**301.3**	-	**302.3**	-	-

but seems to be linked to COVID-19, i.e., a rapid increase of Kawasaki disease related to SARS-CoV-2 had been admitted, starting two weeks after the peak of the COVID-19 epidemic (9). Most children who have been treated for the condition have either tested positive for the COVID-19 infection or have antibodies for it, indicating exposure to COVID-19.

MIS-C cases are presented with signs and symptoms similar to Kawasaki disease and toxic shock syndrome. Fever and gastrointestinal symptoms are the most common signs. The fever is persistent, generally lasting four days or more. Gastrointestinal symptoms, including non-bloody diarrhea, vomiting, and abdominal pain are the most common complaints. Cardiocirculatory manifestations (extended capillary refill time, persistent hypotension, and persistent tachycardia) are rather frequent conditions, while respiratory symptoms seem to be relatively rare. Altered mental status (confusion, somnolence) or syncope may occur. Rash, conjunctivitis, lips or oral cavity changes, hand and feet anomalies (non-specific extremity pain and swelling) and lymphadenopathy have also been observed (10-12).

The primary classification of MIS-C should be based on the presenting phenotype: (A) Kawasaki disease-like – complete and incomplete, classified using the American Heart Association criteria, (B) Non-specific – children presenting with shock or fever, or both, and symptoms that may include abdominal pain, gastrointestinal, respiratory, or neurological symptoms that do not meet the criteria for Kawasaki disease (13).

Laboratory and instrumental results have shown that neutrophilia and lymphopenia are typical in CBC, including the presence of anemia and thrombocytopenia. Blood chemistry shows hypoalbuminemia, hyponatremia, elevated creatinine levels, blood urea nitrogen, transaminases, lactate dehydrogenase and creatine kinase. Inflammatory markers like C-reactive protein, ESR, ferritin, and procalcitonin levels, interleukin-6 are typically elevated. Laboratory markers of inflammation correlate with the disease severity (14). In coagulation studies, the prothrombin time and international normalized ratio, partial thromboplastin time, D-dimer, and fibrinogen levels may also be elevated. Cardiac markers high-sensitive troponin and the N-terminal pro-B-type of the natriuretic peptide may be markedly elevated.

SARS-CoV-2 test involving the RT-PCR, antigen, or specific antibody test results are almost always positive in nearly all patients; however, negative test results do not exclude the disease (15).

Chest radiography may reveal rare unilateral or bilateral infiltrates and pleural effusion. ECG may reveal heart block (1st, 2nd, or 3rd degree), increased QT interval, ventricular arrhythmias, and ST-segment elevation. The echocardio-

gram shows features of myocarditis (left ventricular systolic dysfunction) and additional changes characteristic of Kawasaki disease (coronary artery dilation, valvulitis, mitral regurgitation, pericardial effusion). Finally, the abdominal ultrasound shows hepatosplenomegaly, lymphadenopathy, bowel wall edema and terminal ileitis, gallbladder edema, or ascites.

In terms of health management, the location of care should be determined by the severity of the disease. Children exhibiting a complete or incomplete Kawasaki disease-like phenotype can receive care in a local hospital without a PICU. If not experiencing single or multiple organ dysfunction or cardiac involvement, they can undergo an echocardiogram by a clinician competent in assessing cardiac symptoms including coronary artery abnormalities.

Escalation to a PICU that has clinicians with cardiology expertise should be considered early for any child with single or multiple organ dysfunction.

Children showing any evidence of cardiac involvement should be cared for in a high dependency paediatric unit or PICU with clinicians who have cardiology expertise (8).

Caring for children with MIS-C and experiencing features of Kawasaki disease-like (complete and incomplete) phenotype requires immunobiological therapy.

First-line therapy for all children is intravenous immunoglobulin (2 g/kg), administered in a single or divided dose depending on the clinical picture and cardiac function. High-risk children (younger than 12 months and those with coronary artery changes) should be given early intravenous methylprednisolone (10-30 mg/kg, in addition to intravenous immunoglobulin).

Second-line therapy is based on intravenous methylprednisolone (2–30 mg/kg) for children who remain unwell 24 hours after infusion of intravenous immunoglobulin, particularly if they have ongoing pyrexia. Gastric protection (e.g., omeprazole) should be given to children on high-dose steroids.

Biological therapy should be considered a third-line option in children who do not respond to intravenous immunoglobulin and methylprednisolone. The preferred biological therapy for children is infliximab.

The same care is administered to children with a non-specific presentation phenotype of MIS-C who exhibit coronary artery abnormalities, including toxic shock syndrome, progressive disease, and extended duration of fever (>5 days).

Antiviral and antibiotic therapy includes remdesivir as the first-choice antiviral therapy for children who are SARS-CoV-2 positive. Intravenous antibiotics should be commenced in all patients (based on the clinical picture and culture results). Children with toxic shock syndrome should be given clindamycin in addition to broad-spectrum antibiotics.

Antiplatelet and anticoagulation therapy includes treatments for children older than 12 years, requiring that they wear compression stockings. Low-dose aspirin (3-5mg/kg/day to 80 mg/day) should be continued for a minimum of 6 weeks in all patients. Aspirin is not indicated in children with acute bleeding or thrombocytopenia less than 80×10^9/L. Children who have a thrombotic event should follow the local protocol for care in such cases. A haematologist should examine children with abnormal coronary arteries regarding long-term antiplatelet and anticoagulation therapy (8).

CONCLUSION

Children with MIS-C present symptoms more severe than children with COVID-19. Fever and gastrointestinal symptoms are the primary manifestations followed by multisystem involvement, particularly the cardiovascular system. A timely diagnosis of this rare but potentially severe disease is important for adequate treatment. Longer follow-up and further research on the outpatient management of MIS-C are needed.

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SAŽETAK

Slučaj multisistemskog upalnog sindroma kod djece vremenski povezanog sa SARS-CoV-2

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Uvod. COVID-19 u djece je relativno blaga bolest. Međutim, ozbiljnije stanje koje karakterizira upalni sindrom u obliku Kawasakijeve bolesti nazvane multisistemski upalni sindrom kod djece a koja je vremenski povezana s infekcijom SARS-CoV-2 je ponešto rjeđa patologija.

Izvješće o slučaju. Prikazan je klinički slučaj multisistemskog upalnog sindroma kod djeteta koji je vremenski povezan s infekcijom SARS-CoV-2 u prethodno zdrave djevojčice predškolske dobi. Bolest je imala nepotpuni oblik sličan Kawasakijevoj bolesti koji je odgovarao kriterijima SZO-a i CDC-a za ovaj sindrom u djece i adolescenata.

Zaključak. Ovaj klinički slučaj skreće pažnju liječnika opće prakse i pedijatara na osobitosti dijagnosticiranja i liječenja ovog sindroma.

Ključne riječi: COVID-19; MULTISISTEMSKI UPALNI SINDROM KOD DJECE, POVEZAN S COVID-19; DIJETE