Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Clinical Characteristics of Pediatric Inflammatory Multisystem Syndrome Associated With COVID-19

Leila Shahbaznejad
Pediatric Infectious Diseases Research Center, Communicable Diseases Institute, Mazandaran University of Medical Sciences, Sari, Iran.
Mohammad Reza Navaifar
Pediatric Infectious Diseases Research Center, Communicable Diseases Institute, Mazandaran University of Medical Sciences, Sari, Iran.
Ali Abbaskhanian
Pediatric Infectious Diseases Research Center, Communicable Diseases Institute, Mazandaran University of Medical Sciences, Sari, Iran.
Fatemeh Hosseinzadeh
Pediatric Infectious Diseases Research Center, Communicable Diseases Institute, Mazandaran University of Medical Sciences, Sari, Iran.
Mohammad Sadegh Rezai (drmsrezaii@yahoo.com)
Pediatric Infectious Diseases Research Center, Communicable Diseases Institute, Mazandaran University of Medical Sciences, Sari, Iran.
https://orcid.org/0000-0003-4585-9954

Research article

Keywords: Pediatric Inflammatory Multisystem Syndrome, Children, COVID-19, Case report

DOI: https://doi.org/10.21203/rs.3.rs-51157/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License

Abstract

Background: Although symptoms and signs of COVID-19 (Coronavirus disease 2019) in children are milder than adults, there are reports of more severe cases which was defined as pediatric inflammatory multisystem syndrome (PIMS). The purpose of this report is to describe possible association between COVID-19 and PIMS in children.

Methods: From 28 March to 24 June 2020, 10 febrile children were admitted with COVID-19 infection showing characteristics of PIMS in a tertiary hospital in the north of Iran. Demographic and clinical characteristics, laboratory and imaging findings and therapeutic modalities were recorded and analysed.

Results: The mean age of patients was 5.37±3.9 years (13 months to 12 years). Six of them were boy. Kawasaki disease, myocarditis, toxic shock syndrome, appendicitis, sepsis, urosepsis, prolonged febrile seizure, acute hemorrhagic edema of infancy, and COVID-19-related pneumonia were their first impression. All of them had increased C-reactive protein level and most of them had an elevated erythrocyte sedimentation rate, lymphopenia, anemia, and hypoalbuminemia. Some of them had thrombocytopenia. Six of them were serologically or polymerase chain reaction positive for COVID-19, and 4 of them were diagnosed as COVID-19 just by chest computed tomography scan. Most of the patients improved without a residual sequel, except one who died with multiorgan failure and another case discharged with a giant coronary aneurysm.

Conclusion: Children with COVID-19 may present symptoms similar to Kawasaki disease and inflammatory syndromes. PIMS should be considered in children with fever and rash, seizure, cough, tachypnea, and gastrointestinal symptoms such as vomiting, diarrhea, and abdominal pain.

Background

In January 2020, China reported a novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). The world is currently in the rapid emergence of the pandemic caused by SARS-CoV-2 now which is called COVID-19 (Coronavirus disease 2019) (2). The real incidence of this infection in children is indefinite. The most common presentations of COVID-19 are fever and cough, however, the disease can have other manifestations such as myalgia, headache, dizziness, vomiting, diarrhea, and abdominal pain. Despite the lack of the full presentation of disease and outcome data in children, the most commonly reported symptoms and signs are milder than adults (3). This may be due to differences in immune responses to the virus (4).

Unusual cases of the COVID-19 with signs and symptoms similar to atypical Kawasaki disease (KD) and toxic shock syndrome (TSS) have been reported recently (5–7). In April 2020, the first report of a child with Kawasaki disease and concurrent positive reverse transcriptase polymerase chain reaction (RT-PCR) of COVID-19 was published in the United States (8). Since this first report, other countries have reported some cases with prolonged fever, dyspnea, irritability, diarrhea, vomiting, abdominal pain, as well as conjunctivitis, rash, and cardiogenic shock (6, 7, 9). According to these reports, world health organization (WHO) and center of disease control and prevention (CDC) of some countries shared a clinical guideline as Pediatric inflammatory multisystem syndrome (PIMS) (10–12).

WHO provided a preliminary case definition criterion for PMIS in children and adolescents 0–19 years of age with fever > 3 days AND two of the following: a) Rash or bilateral non-purulent conjunctivitis or mucocutaneous inflammation signs (oral, hands or feet); b) Hypotension or shock; c) Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including Echocardiography findings or elevated Troponin/NT-proBNP); d) Evidence of coagulopathy (by PT, PTT, and elevated d-Dimers); e) Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain) and elevated markers of inflammation such as ESR, C-reactive protein (CRP), or procalcitonin. AND Elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin. AND No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes. AND Evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19 (11).

A possible temporal causality between COVID-19 and PIMS has been hypothesized because some of the children tested for COVID-19 infection were either positive by polymerase chain reaction (PCR) or serology (5, 7). There are limited relevant evidence and no concrete working hypothesis for pathogenesis, to examine the association between exposure to COVID-19 and PIMS. Immune response to COVID-19 involves both cell-mediated immunity and antibody production. Based on previous in vitro studies, antibodies to the spike protein may improve the ability of novel strains of the coronavirus to enter cells. In COVID-19 infection, one suggestive mechanism that causes PIMS in children could be via antibody-dependent enhancement (7).

Early diagnosis and management of PIMS are very critical in order to decrease the risk of long-term complications, morbidity and mortality. We lack knowledge about COVID-19-induced presentations, mimic other diseases like status epilepticus and acute abdomen, immune responses, and how they may relate to PIMS. Therefore, the management of PIMS remains unclear and difficult. The purpose of this report is to provide a description and characterization of PIMS, increase the level of evidence about the possible association between COVID-19 and PIMS in our pediatric referral hospital in the north of Iran, focusing on the mode of novel manifestations and best practice of suspected PIMS condition and early outcome.

Methods

From 28 March to 24 June 2020, 10 febrile children were admitted with COVID-19 infection showing characteristics of PIMS (10–12) in a tertiary hospital in the north of Iran, Mazandaran province, Sari. Demographic and clinical characteristics, laboratory and imaging findings and also therapeutic modalities were recorded in all of them, separately. In this manuscript, we reported the most compatible clinical syndrome as the first impression in each case, complications and final outcome in detail. For detection of SARS-CoV-2 infection in our patients, in addition to chest CT scan, we used COVID-19 real-time polymerase chain reaction (Made by Roge Network Technology and Sansure Biotech Inc., China), serum immunoglobulin M and G: IgM and IgG (Made by Pishgam Teb Co, Tehran, Iran). The ethics committee of Mazandaran University of Medical Sciences approved the study protocol (No = IR.MAZUMS..REC.1398.7277). Written informed consent was obtained from parents of all patients prior to treatment.

Results

Case 1

A 12 year-old boy with history of chronic renal failure and recurrent hemodialysis, admitted with fever and chills from 7 days ago, rash from 3 days ago which disappeared before admission, diarrhea, weakness, and fatigue without respiratory complaints. He was toxic at admission time and vital signs were unstable: Temperature: 39.5 ^{o}c, blood pressure: 70/50 mmHg, heart rate: 120/min and SPO2: 92% in the ambient room. He didn't have tachypnea or abnormal lung sounds. Hours later, he developed respiratory distress. Vasoactive drugs, oseltamivir, meropenem, vancomycin, hydroxychloroquine, and Kaletra were prescribed. In the chest computed tomography (CT) scan, patchy ground-glass opacity and interlobar septal thickening were found compatible with COVID-19. In the complete blood count (CBC), lymphopenia, anemia, and thrombocytopenia were seen. Raised blood urea and creatinine, increased liver transaminases, proteinuria, hematuria, and marked acidosis in the arterial blood gas (ABG) were also noted, but creatine phosphokinase (CPK), lactate dehydrogenase (LDH), and electrolytes were in normal values. The patient's general condition got worse and he underwent tracheal intubation. Echocardiography showed mild mitral and tricuspid regurgitation, mild diastolic dysfunction, decreased left ventricular ejection fraction on the first day which deteriorated on the second day (Table 1). Packed red blood cell (packed cell), intravenous immunoglobulin (IVIG), and hydrocortisone prescribed. Before completion of the IVIG infusion, the patient's condition got worse and he died on the third day after hospitalization. Result of COVID-19 RT-PCR was positive for him.

Table 1
Clinical, para clinical and therapeutic data in 10 patients with Pediatric Inflammatory Multisystem Syndrome (PIMS) Associated

Number of case, age, sex, date of admission	COVID-19 test	First presentation symptoms and signs	Ongoing presentation	Abdomino pelvic Ultrasonography	Chest imaging	Echocardiography	Laboratory data at admission	Ongoing laboratory data	treatm
Case 1: 12 years old boy, 28 march	Covid-19 RT- PCR: positive	fever and chills, rash, diarrhea, fatigue, toxic appearance	Second day: respiratory distress, heart and respiratory failure		Chest CT-scan: patchy ground glass opacity and interlobar septal thickening	**First day**: mild MR, Mild TR, mild diastolic dysfunction, LVEF 50%, **Second day**: moderate MR and TR, moderate diastolic dysfunction LVEF 30%	CBC: WBC: 8.7, N: 90, L: 10, Hb: 9.5, Plt: 75, CRP: 1+, ESR: 32, urea: 75, Cr: 2.5, AST: 62, ALT: 30, UA: Pro: 1+, WBC: many, RBC: 10–12 ABG: PH: 7.2, Hco3: 11.8, Pco2: 30, Po2: 32	Cr: 3.2, urea: 126, D. dimer: 6888, CRP: 50	Vasoac Oseltar merope vancor hydrox Kaletra hydroc 2 mg/k packed
Case 2: 5 years old girl, 8 April	COVID-19 RT-PCR positive	Fever, vomiting, diarrhea and skin rash, cough and otalgia, conjunctivitis, Loss of appetite	3 to 5 days after admission: Tachypnea, drowsiness, generalized edema, headache, myalgia, pharyngeal congestion, purulent conjunctivitis, Abdominal pain	mild to moderate free fluid in abdomen and bilateral mild to moderate plural effusion	Normal CT-scan at admission. But on day 5, bilateral plural effusion and patchy infiltration, ground glass apearance	mild TR, trivial MR, normal coronary arteries on 2 occasion	CBC: WBC: 8.1, N: 60, Hb: 10, , Plt: 150, ESR: 71, CRP:28, Alb: 2.6	CBC: WBC: 6.6, N: 74, L: 20, Hb: 7.4, Plt: 86, ESR: 28, CRP: 23, Alb: 2.2, total protein: 4 Vitamin D: 15	Hydrox Azithro Ceftria change merope 1gr/kg, Red Pa
Case 3: 13 months old boy, 13 April	COVID-19 RT-PCR positive	Fever, generalized erythematous patches, papule and some target shape lesion on edematous base	3 days after admission, Respiratory distress, decrease spo2: 84% in ambient room and generalized edema	mild intra-abdominal fluid	at admission: Normal chest CT-scan. At day 3: Chest CT-scan: bilateral plural effusion, basilar patchy infiltration and reverse halo sign	Mild TR, mild MR and normal coronary arties on 2 occasion	CBC: WBC: 8.2, N: 65, Hb: 10.8, PLT: 189, Alb: 3.4 ESR: 54, CRP: 96	day 3: CBC, WBC: 14.5, N: 58, L: 29, Hb: 7.5, Plt: 141 ESR: 60, CRP: 26, Alb: 2.2,	hydrox Ceftria change merope Vancor 1gr/kg, Red Pa
Case 4: 10 years old girl, 27 April	COVID-19 IgG: positive	Fever, itching skin rash, maculopapular and target shape rashes with more accumulation around neck and trunk and axilla cough, abdominal pain, oliguria, bilateral non purulent conjunctivitis, hypotension and toxic appearance	Generalized edema, right leg edema and sever pain, mild plural effusion	Urinary system ultrasonography was normal, color Doppler ultrasonography of lower limbs veins were normal	CXR and Chest CT-scan before admission: NL Chest CT-scan at day 4: COVID-19 compatible changes and mild bilateral plural effusion	mild MR, mild TR, Mild PI, EF: 60–64% in 3 occasion	CBC: WBC: 9, N: 69, L: 10, Hb: 7.5, Band: 12, Plt: 130, ESR: 30, CRP: 36, Urea: 78, cr: 2.3,, D Dimer: 6556 Alb: 2	Third day: CBC: WBC: 13.9, N: 87 L: 6 Hb: 9.6 Plt: 211	merope clindar vancor vasoac 1 g/kg, cell, alb enoxap Vitamir

Number of case, age, sex, date of admission	COVID-19 test	First presentation symptoms and signs	Ongoing presentation	Abdomino pelvic Ultrasonography	Chest imaging	Echocardiography	Laboratory data at admission	Ongoing laboratory data	treatm
Case 5: 14 months old boy, 3 May	COVID-19 RT-PCR negative, IgM: positive	fever, irritability, macoulopapolar erythematous rashes, edema of hands and feet, Cracked and erythematous lips, erythematous tongue and bilateral non purulent conjunctivitis	Irritability, abdominal distension, giant coronary aneurysm	Liver span: 117 mm, spleen: 98 mm, greater than normal, mild intra-abdominal fluid, mild bilateral plural effusion	First day: CXR normal, Chest CT-scan showed non-significant changes Day 4: chest CT-scan: non-significant changes	First day: normal coronary arteries, minimal right Pleural effusion (5 mm), minimal MR, good EF	CBC: WBC: 22, N: 83, L: 5, 6, Band: 5, Hb: 10.6, plt: 197, ESR: 65, CRP: 38, Na: 129, AST: 200, ALT: 197, Alb: 2.3, PTT: 50, PT: 18, INR: 2	Day 4: WBC 21.8, N: 79, L: 15, Hb: 8.7, Plt: 224, Alb: 3.2, AST: 57, ALT: 55, PT: 14.8, PTT: 42, INR: 1.3, Day 14: CBC: WBC: 25.7 N: 38, L: 44, Mono: 17, Hb: 11.6, Plt: 1168 CRP: 10.9, ESR: 25	IVIG 2 g Aspirin hydroxy zinc, Vi Cefota change merope vancor Albumi cell, me prednis 2 mg/k vasoac heparir inflixim
Case 6: 6.5 years old boy, 4 May	COVID-19 RT-PCR negative, COVID-19 IgG positive	fever, anorexia abdominal pain, vomiting, loose defecation, erythematous rash around feet, hands, trunk and perioral, periorbital edema, erythema of oropharynx, right TM erythema	At day 2: dyspnea, repertory distress, spo2 87%, mild abdominal distension, irritability, anasarca edema	spleen: 117 mm, more than normal with normal parenchymal echo, free interloop fluid, sub hepatic and sub splenic, several reactive lymph nodes 15*7 mm in para aorta and peripancreatic	At admission: Chest CT, non-significant changes for COVID-19 At day 4: Chest CT-scan bilateral opacities compatible with COVID-19	Day 2: minimal TR Day 4: mild TR, trivial MR	CBC: WBC: 4.7 N: 77, L: 14, band: 3, Hb: 10, Plt: 121, ESR: 48, CRP: 45, UA: blood: trace, WBC: 8–10,	CBC: WBC: 6.93 Hb: 7.8 Plt: 73 L: 14 N: 80 Alb: 2.3 CRP: 39 ESR: 58	Ceftria Vancor Merope hydroxy packed Albumi
Case 7: 7.5 year old girl 4 May	COVID-19 RT-PCR negative	fever, irritability, abdominal pain, myalgia, vomiting, diarrhea and generalized erythematous maculopapular and patches	Facial edema, tachypnea and tachycardia developed and the patient got toxic with gallop in heart auscultation	Normal	Admission Chest CT: NL CXR: at day 3: bilateral mild Ground Glass opacity	Day 3: Mod MR, TR, low EF 50%, Dilated RV, LV: myocarditis Day 7: moderate MR, mild Pleural effusion, low LVEF, lack of tapering, brightness in RCA and LAD compatible with KD and Myocarditis	CBC: WBC: 9.8, N: 89, L: 10, Vitamin D: 4 ng/ml AST:93 ALT: 69	CBC: WBC: 13.3 Hb: 7.5, Plt: 213 N: 85 L: 10 Alb: 1.9, ESR: 73, CRP: 35 Urea: 72 Cr: 1.1	Ceftria change Vancor Merope hydroxy Zinc, V magne packed Albumi IVIg: 2
case 8: 20 months old boy, 9 may	COVID-19 RT-PCR negative, COVID-19 IgG, IgM negative	Fever, coryza, vomiting diarrhea, abdominal pain, irritability during urination and loss of appetite, erythematous papule in 2 centimeter diameter in the forehead, erythema of oropharynx	tachypnea with unilateral tongue swelling and drooling, with discrete ulcers under the tongue	Normal	Chest CT: bilateral ground opacity compatible with COVID-19	lack of tapering in RCA and LAD, Mild dilatation of LA, LMCA: 3.7 mm, RCA: 2.2, LAD: 2.2, perivascular brightness around LAD, moderate MR, diastolic dysfunction	WBC: 52.5, N: 80, L: 10, band: 4, Hb: 9.5, Plt: 932, ESR: 100, CRP: 1+ SE: WBC: 4–5, RBC: 2–3	ABG: PH: 7.33, Pco2: 37, HCO3: 19.9, PO2: 71, Alb: 2.5	Ceftria change clindar Merope hydroxy Zinc, V 2 g/ kg 80 mg/

Number of case, age, sex, date of admission	COVID-19 test	First presentation symptoms and signs	Ongoing presentation	Abdomino pelvic Ultrasonography	Chest imaging	Echocardiography	Laboratory data at admission	Ongoing laboratory data	treatm
Case 9: 7 years old boy, 23 may	COVID-19 IgM and IgG and RT.PCR negative	Fever with epigastric pain which shift to Right Lower Quadrant, nausea, vomiting	ill, abdominal distension and recurrent vomiting	Reactive lymph node, max diameter 6 mm, fat stranding in Right Lower Quadrant and free inter loop fluid	Chest CT: sub plural atelectasis, mild bilateral pleural effusion, some nodular like lesions in both inferior lobes of lungs compatible with COVID-19	NL	CBC: WBC: 24000, L: 6%, N: 90%, band: 4%, Hb: 11, Plt: 356, ESR: 72, CRP: 2+	Day 2: CBC: WBC: 13.5, N: 77, L: 10, Mono: 11, Hb: 10.3, Plt: 347, ESR: 90, CRP: 25 Alb: 3.2	Meroni Ceftria to mero hydrox Vitamir
Case 10: 18 months old girl 13 June	RT- PCR COVID-19 positive	Fever and status epilepticus	Second day: ill and lethargic, maculopapolar blench able rash, tachypnea		CXR: nl Chest CT in 2 occasion: bilateral nonspecific opacity in inferior lobes	Normal	CBC: WBC: 8.5, N: 80%, L: 14%, Hb: 11.8, PLT: 160 ESR: 15, CRP: 16 Alb: 2.3	WBC: 1.88, N: 34, L: 59, M: 5, Hb: 10.2, plt: 103 CRP: 3 Alb: 2.5	Merope clindar phenob hydrox Vitamir Albumi 1 g/kg,

ABG: Arterial blood gas

Alb: Albumin, grams per deciliter

Alt: Alanine aminotransferase, units per liter

AST: Aspartate aminotransferase, units per liter

CBC: Complete blood count

Chest CT-scan: Chest computed tomography scan

COVID-19: Coronavirus disease 2019

Cr: Creatinine, milligrams per deciliter

CRP: C reactive protein, milligram per liter

CXR: Chest roentgenogram

D-dimer: ng/mL, increased level > 500,

ESR: Erythrocyte sedimentation rate, millimeters per hour

Hb: Hemoglobin, grams per deciliter

IgM: Immunoglobulin M

IgG: Immunoglobulin G

INR: International normalized ration

IVIG: Intravenous immunoglobulin

KD: Kawasaki disease

L: Lymphocyte, %

LAD: Left anterior descending artery

LMCA: Left main coronary artery

LVEF: Left ventricular ejection fraction

Mono: Monocyte, %

MR: Mitral regurgitation

NA: Not assessed,

Number of case, age, sex, date of admission	COVID-19 test	First presentation symptoms and signs	Ongoing presentation	Abdomino pelvic Ultrasonography	Chest imaging	Echocardiography	Laboratory data at admission	Ongoing laboratory data	treatm
N: Neutrophil%									
Na: Sodium, mill equivalents per liter									
NL: Normal									
Plt: Platelet, × 10^9/Liter									
PICU: Pediatric intensive care unit									
Pro: Protein									
PT: Prothrombin time, seconds									
PTT: Partial thromboplastin time, seconds									
RCA: Right coronary artery									
RT-PCR: Reverse transcription polymerase chain reaction									
SARS-CoV-2: Acute respiratory syndrome coronavirus 2									
TR: Tricuspid regurgitation									
Total protein: Grams per deciliter									
Urea: Milligrams per deciliter									
Vitamin D, ng/mL									
WBC: White blood cell, × 10^9/Liter									

Table 2
Wrap up data of hospitalized patients with Pediatric Inflammatory Multisystem Syndrome (PIMS) Associated with SARS -CoV-2, N: 10

Demographic Data		**Laboratory abnormalities**		**COVID-19 Diagnostic measures**	
Gender: girl/boy	4/6	lymphocyte > 1000/µL	8	COVID-19 RT-PCR	3
Age	5.37 ± 3.9 (13 months to 12 years old)	Hb < 10 g/dl	8	COVID antibodies	3
Clinical Data		Plt < 100000/µL	3	Just chest CT-scan	4
Duration of fever	9.4 ± 1.77 (6–12) days	ESR > 30 mm/hour	9	**Treatments**	
Skin rash (Total)	8	CRP > 10 mg/L	10	Antibiotics	10
Maculopapular	8	Albumin < 3 g/dL	8	Hydroxychoroquine	9
Target shape	2	AST or ALT > 50 U/L	2	Packed cell	7
Conjunctivitis(Total)	3	Blood group/RH	1	Albumin	7
Purulent	2	A+	2		
Non-purulent	1	B+	4		
Respiratory symptom (Total)	8	O+	3	IVIG 1 g/kg	6
At admission	3	NA		IVIG 2 g/kg	3
During admission	8			steroid	2
				Vasoactive drugs	4
		Imaging Data		Infliximab	1
Ear drum erythema	3	Plural effusion	4	**Hospital stay**	
Oral mucosal change	4	Intra-abdominal fluid	5	PICU stay (9)	7.8 ± 5.2 days (2–20 days)
Gastrointestinal involvement (Total)	9	Abnormal coronary arteries*	3	Total hospital stay	11 ± 5.5 (3–24) days
Vomiting	5				
Diarrhea	6				
Abdominal pain	7				
Edema	6	Low cardiac ejection fraction*	3	**First impression**	
		Chest CT-scan**	8	Acute hemorrhagic edema of infancy	1
		Normal at admission time	2	Appendicitis	1
		COVID-19 Compatible at the admission time	5	COVID-19	1
Seizure	1	Became COVID-19 compatible in the days after		Kawasaki disease	2

Demographic Data		Laboratory abnormalities	COVID-19 Diagnostic measures	
			Myocarditis	1
			Prolonged febrile seizure	1
			Sepsis	1
Lymphadenopathy	0		Toxic shock syndrome	1
Acute Renal failure	2		Urosepsis	1
Shock	2			
*: Echo cardiography performed for all of ten. ** Chest CT-scan performed for all the cases				
ALT: Alanine aminotransferase, AST: Aspartate aminotransferase,				
Chest CT-scan: Chest computed tomography scan				
COVID-19: Coronavirus disease 2019				
CRP: C reactive protein				
ESR: erythrocyte sedimentation rate				
Hb: hemoglobin,				
IVIG: Intravenous immunoglobulin				
NA: not assessed, PICU: pediatric intensive care unit,				
PICU: Pediatric intensive care unit				
Plt: platelet				
SARS -CoV-2: acute respiratory syndrome coronavirus 2				

Case 2

A 5 year-old girl presented with a history of 3 days high-grade fever (39–40 ^{o}c), vomiting and one episode of skin rash during fever, loss of appetite, intermittent cough, otalgia, and diarrhea. On admission, she was ill and irritable without respiratory distress and SPO2 was 99% in room air. She had bilateral otitis and bilateral non-purulent conjunctivitis. Her parents had a suspicious history of COVID infection, so the chest CT-scan was performed and was normal. Treatment with ceftriaxone and zinc gluconate started. Gradually, picture of the disease changed and preorbital edema (day 3), headache, limb pain, pharyngeal congestion with punctuated exudate and purulent conjunctivitis occurred. Due to abdominal pain and tenderness, abdomino-pelvic ultrasonography was performed which was normal, just mild to moderate free fluid was seen and also, mild to moderate bilateral pleural effusion was detected. Liver transaminases, serum amylase and lipase were in normal range. Because of a family history of COVID-19 infection and new changes in the second chest CT-scan compatible with COVID-19 infection, hydroxychloroquine and azithromycin started at the 3rd day and the patient was isolated. At day 5, COVID-19 RT-PCR result was positive, she was still febrile and her condition has deteriorated. She became drowsy, tachypneic (respiratory rate: 38 /min) without retraction and dry cough and generalized edema developed. She had SPO2 = 88% on room air. So, she was transferred to the pediatric intensive care unit (PICU). On CBC, severe anemia and thrombocytopenia in addition to hypoalbuminemia were noted (Table 1). So, packed red blood cells (packed cell), 1 g/kg IVIG and albumin were transfused and antibiotics changed to meropenem. Blood urea, Cr, LDH, peripheral blood smear, prothrombin time (PT), partial thromboplastin time (PTT), bilirubin, triglyceride, and fibrinogen level were in the normal range and urine analysis was normal. Blood and urine cultures were negative for any organism. Echocardiography showed mild tricuspid regurgitation, trivial mitral regurgitation with normal coronary arteries. During the first 8 days, fever subsided, but the patient was still tachypneic. Finally, the patient discharged after 13 days with a good general condition.

Case 3

He was a 13 month-old boy presented with a 4-day history of fever and 3 days of rash. Skin rash started from palms of the hands and the soles of the feet and then, erythematous patches, papule, and some target shape lesions on edematous base on the trunk, limbs and face developed without itching sensation. He also defecated loose stool 2 to 3 times and had loss of appetite and irritability without any respiratory complaints except left tympanic membrane erythema. His parents worked in a COVID-19 referral ward. On admission day, chest CT-scan was normal and he was treated with hydroxychloroquine and ceftriaxone. On day 3, the patient's condition deteriorated, generalized edema, purulent conjunctivitis, respiratory distress with tachypnea, intercostal and subcostal retraction occurred. While SPO2 was 84% in the ambient room, the second chest CT-scan changed to typical COVID-19 findings (bilateral pleural effusion, basilar patchy infiltration, and reverse halo sign). Anemia and hypoalbuminemia occurred while both were in the normal range at the admission day (Table 1). So, the patient transferred to the PICU, and oxygen was administered with a hood and packed cell, albumin and IVIG (1 gr/kg) transfused. Antibiotic was changed to meropenem and vancomycin. Abdominopelvic ultrasonography was normal, just mild fluid in sub-hepatic, peri-splenic, and interloop space were seen. Echocardiography showed mild tricuspid and mitral regurgitation and normal coronary arteries on two occasions. The patient gradually improved, skin rashes got better, he became afebrile and without any distress. He discharged after 8 days and COVID-19 RT-PCR result was positive for him.

Case 4

A 10 year-old girl presented with fever and itching skin rash from 5 days ago referred. One day before admission, her general condition worsened; she got toxic and cough, abdominal pain, and generalized edema and oliguria developed. The skin rashes were maculopapular and target shape rashes with more accumulation around neck, trunk, and axilla. Mucous membranes were intact except for bilateral conjunctivitis and cracked lips. SPO2 was 90% in room air, blood pressure: 66/44 mmHg, pulse rate: 120 /min and respiratory rate: 36 /min. In the laboratory evaluations, anemia, hypoalbuminemia, and impaired renal function tests were noted (Table 1). According to hypotension and shock state, vasoactive drugs started in addition to meropenem, clindamycin, vancomycin, IVIG, packed cell, and albumin (Table 1). The hemodynamic status of the patient got stable after 3 days. Liver transaminases, PT, PTT, CPK, troponin, LDH, fibrin degradation products (FDP), C3, C4, and CH50 were in normal range. Antistreptolysin O, antiphospholipid antibody, and antinuclear antibody (ANA) were negative too. Blood and urine culture were also negative. Chest CT-scan before admission and chest roentgenogram (CXR) at admission day were normal. COVID-19 RT-PCR result was negative but COVID-19 immunoglobulin G (IgG) was positive, which was measured a week later. On day 3, the patient complicated with edema, severe pain of right lower extremity, and venous stasis due to placement of central vein catheter of right femoral vein. Color doppler ultrasonography of lower limb veins was normal. Enoxaparin was started as prophylaxis of deep vein thrombosis (DVT). Chest CT-scan at day 4 showed COVID-19 compatible changes with mild bilateral pleural effusion. The urinary system ultrasonography was normal. Echocardiography reported mild tricuspid regurgitation, mild mitral regurgitation, mild pulmonary insufficiency, and normal ejection fraction on 3 occasions. Fever subsided 4 days after admission, vitamin D, and zinc gluconate were added to the patient's drugs. The general condition improved and inotrope drugs discontinued gradually. After 11 days, the patient discharged with complete improvement.

Case 5

He was a 14 month-old boy, presented with fever and irritability from 5 days and skin rash from 3 days ago. Maculopapular erythematous rashes first presented from the trunk and upper limb and then generalized and edema of hands and feet developed. Cracked and erythematous lips, erythematous tongue, and bilateral non-purulent conjunctivitis also happened. During the first admission day, the patient became toxic and transferred to the PICU. The CBC showed leukocytosis with significant neutrophil count. Elevated ESR, CRP, and liver transaminases and hypoalbuminemia were found. Urine analysis was normal. COVID-19 RT-PCR was negative, CXR was normal and Chest CT-scan showed non-significant changes. So, cefotaxime, hydroxychloroquine, 2 gr/kg IVIG and 60 mg/kg aspirin, zinc, vitamin D, and albumin started. Echocardiography in the first day showed normal coronary arteries, minimal right pleural effusion (5 mm), minimal mitral regurgitation without coronary artery abnormality. Because of prolonged PT and PTT, fresh frozen plasma (FFP), and vitamin K prescribed. Fever continued 2 days after IVIG infusion, and he was still toxic. So, the second dose of IVIG was infused in the fourth day of admission. Echocardiography in that time showed diastolic dysfunction, mild right and left coronary artery dilatation in left anterior descending artery (LAD) and left circumflex artery without aneurysm. Liver transaminases, PT and PTT decreased to the normal level but leukocytosis continued and packed cell transfused for severe anemia, and ceftriaxone changed to vancomycin and meropenem. The second chest CT-scan showed non-significant changes. While fever subsided at day 7, hydroxychloroquine discontinued, but echocardiography showed progression in coronary arteries dilatation, moderate mitral and tricuspid regurgitation, decreased ejection fraction, and mild diastolic dysfunction, so 2 mg/kg/day prednisolone, vasoactive drugs and furosemide started. On day 10, the patient got hemodynamically stable, so vasoactive drugs tapered but abdominal distension occurred with non-significant findings in the examination. Ultrasonography showed mild hepatosplenomegaly, mild intra-abdominal fluid, and mild bilateral pleural effusion. The CBC showed leukocytosis and initiation of thrombocytosis (platelet count: 420.000/μL). Echocardiography showed progressive coronary artery aneurysm and beading and clopidogrel started. Abdominal distension improved during the last 5 days, and the skin rash disappeared with pilling on day 14. Still afebrile, he was toxic. COVID-19 RT-PCR result was negative but COVID-19 IgM was positive. After that, marked thrombocytosis appeared in the CBC (platelet count: 1.168.000/μL), ESR and CRP normalized but coronary artery dilatation progressed to a giant aneurysm in day 17 as follows: right coronary artery (RCA): 8.3 mm, left main coronary artery (LMCA) and LAD: 6.7–7.2 mm with good left ventricular ejection fraction. So, warfarin and infliximab prescribed. The patient discharged from the hospital with aspirin and warfarin. Results of other evaluations during admission like serum vitamin D, LDH, CPK, and antiphospholipid antibodies were unremarkable. Two weeks later, the coronary diameters decreased to 6 mm in RCA and near to 5 mm in LMCA and LAD in follow-up echocardiography.

Case 6

A 6.5 year-old boy, presented with a history of 3 days fever, anorexia, and abdominal pain in periumbilical and hypogastric area with occasional vomiting (3 times), one loose defecation, and skin erythematous rash around ankles which spread to the trunk. He had no respiratory complaints and received a suppository of diclofenac and acetaminophen for pain and fever relief. He had a history of repaired duodenal atresia at birth. On physical exam, the patient was ill and febrile, had macular erythematous rashes around feet, hands, trunk and perioral, periorbital edema, erythema of oropharynx, right eardrum erythema and hypogastric tenderness. He had elevated ESR and CRP in addition to abnormal urine sediment. Ceftriaxone started and chest CT-scan performed with non-significant changes for COVID-19. Urine culture of the first day was negative. On the second day of admission, the patient got toxic and irritable with respiratory distress, low SPO2: 87%, mild abdominal distension, and anasarca edema. The patient transferred to the PICU. Serum albumin was 2.6 g/dL, while other indexes like amylase and lipase were in normal values. So, albumin started. During the last 2 days, general condition of the patient got worst, he became anemic and more toxic, so albumin, 1 gr/kg IVIG, packed cell, hydroxychloroquine, and vitamin D were administered and ceftriaxone changed to vancomycin and meropenem. A second chest CT-scan showed bilateral opacity compatible with COVID-19. COVID-19 RT-PCR was negative but COVID-19 IgG was positive which was measured a week later. Abdominal ultrasonography showed mild splenomegaly, free interloop fluid, and several reactive lymph nodes. Echocardiography at 2 occasions reported normal coronary arteries. Other investigations like Wright, Widal, blood, urine, and stool culture were negative. Transaminases, PT, PTT, LDH, FDP, and D-dimer were in normal values. The patient's abdominal pain improved at day 6, and he discharged after 11 days.

Case 7

A 7.5 year-old girl presented with a history of fever, irritability, myalgia, vomiting, diarrhea, abdominal pain, generalized erythematous maculopapular and patches from 4 days ago without respiratory complaints. Her parents were infected with COVID-19 nearly 2 weeks ago. She received diclofenac and azithromycin before admission. On physical exam, she was ill with no distress. Erythema of the throat and generalized erythematous maculopapular and patches were observed. At the admission day, lymphopenia and vitamin D deficiency were noted (Table 1). Chest CT-scan, abdominal ultrasonography and stool exam were normal and cultures of the urine, blood, and stool were negative. So, ceftriaxone, hydroxychloroquine, zinc, and vitamin D prescribed. Evaluation for infection with COVID-19 with RT-PCR COVID-19 were negative. At the third admission day, facial edema, tachypnea and tachycardia developed and the patient got toxic with a gallop in heart auscultation. Due to marked hypoalbuminemia and anemia, packed cell and albumin were transfused. Blood urea and Cr raised, with normal values for serum electrolytes, PT, PTT, CPK, LDH, troponin, and liver transaminases. Anti-phospholipid antibodies were negative. Echocardiography showed low ejection fraction with dilated right and left ventricle, so, the diagnosis of myocarditis was raised; vasoactive drugs and 1 g/kg IVIG started and ceftriaxone changed to meropenem and vancomycin with magnesium sulphate for hypomagnesemia. CXR showed bilateral mild ground-glass opacity. Gradually, during last days, facial edema improved a little, but tachycardia and tachypnea was persistent at the 5th day. The second echocardiography report included mild pleural effusion, valve insufficiency, low ejection fraction, lack of tapering and brightness in RCA and LAD. So, another dose of IVIG (1 g/kg) with 60 mg/kg/day aspirin prescribed. With the improvement in the hemodynamic status, vasoactive drugs gradually tapered. On the 7th day, the patient became afebrile and discharged after 12 days with normal echocardiography and laboratory tests.

Case 8

A 20 month-old boy presented with intermittent fever from last week. Gradually, coryza, vomiting, and severe diarrhea, abdominal pain, irritability during urination, and loss of appetite appeared. Before admission, he received metronidazole, cefixime, nalidixic acid, diclofenac, and acetaminophen without improvement. He also had an erythematous papule with 2 centimeter diameter in the forehead and erythema of oropharynx. CBC at admission showed marked leukocytosis, thrombocytosis, anemia, and increased levels of ESR and CRP (Table 1). The stool exam had 4–5 white blood cells and 2–3 red blood cells. PT, PTT were normal and blood levels of creatinine, urea, LDH, and CPK were in normal values. Urine analysis was unremarkable and cultures of blood, urine, and stool were negative. Abdominal ultrasonography was normal but Chest CT-scan showed bilateral ground-glass opacity compatible with COVID-19. So, the patient isolated and ceftriaxone, hydroxychloroquine, vitamin D, and zinc gluconate started. Hours after admission, he got tachypnea and SPO2 was 90% without supplementary oxygen. Unilateral tongue swelling and drooling with discrete ulcers under the tongue were seen. So, he transferred to the PICU and ceftriaxone changed to clindamycin and meropenem. Echocardiography found a lack of tapering in RCA and LAD, mild dilatation of left atrium, and diastolic dysfunction. Before starting 2 g/kg IVIG and 80 mg/kg/day aspirin, fever subsided but he was still toxic. Seven days after admission, the patient's condition improved and the second echocardiography after one week was normal. Results of COVID-19 RT-PCR, IgM, and IgG in the first week of admission were negative.

Case 9

He was a 7 year-old boy with fever from 3 days ago. He also suffered from epigastric pain which was shifted to the right lower quadrant (RLQ) after 2 days and was not associated with eating. He had nausea, vomiting, and normal defecation pattern. He was admitted 10 days ago for acute intravascular hemolysis due to glucose 6 phosphate dehydrogenase deficiency (G6PDd) and fava bean exposure and was treated with packed cell and hydration. In the recent admission, he was ill and febrile without respiratory symptoms. On physical examination, tenderness in RLQ and rebound tenderness were noted. Ultrasonography showed reactive lymph nodes, and free interloop fluid. In the CBC, leukocytosis with a shift to left was found. ESR and CRP were markedly elevated, urine and stool were unremarkable. So, the patient received ceftriaxone plus metronidazole and underwent appendectomy, but normal appendix with some exudative secretion in the peritoneal cavity was seen during the operation. After surgery, the patient's condition got worse and became toxic, developed abdominal distension and recurrent vomiting. Abdominal X-ray was normal and repeated ultrasonography reported mild interloop fluid only. A chest CT-scan showed findings compatible with COVID-19 infection. Ceftriaxone changed to meropenem and vitamin D, hydroxychloroquine, and zinc gluconate started. Three 3 days following admission, his fever subsided and abdominal complaints got better. Other investigations like liver transaminases, serum LDH and echocardiography were normal. After 4 days, the patient discharged. COVID-19 IgM and IgG and RT-PCR during admission were negative.

Case 10

An 18 month-old girl referred for a prolonged febrile seizure. The fever started from 4 days ago and seizure was generalized tonic colonic accompanied with loss of consciousness, upward gaze, and foaming, which lasted for 40 minutes, controlled with diazepam and phenobarbital in another hospital. The family was passenger from another province of Iran. She had an epileptic sister. In physical exam, she was lethargic and febrile without abnormal findings. In the CBC, there was lymphopenia. Cerebrospinal fluid (CSF) analysis and electrolytes were normal and CSF, blood, and urine culture were negative. Serum albumin level was decreased. Meropenem, clindamycin, phenobarbital, hydroxychloroquine, and vitamin D were prescribed. Brain CT-scan and CXR had no pathologic finding and chest CT-scan showed bilateral nonspecific opacity in inferior lobes. She was ill and lethargic during the first two days, so albumin, 1 g/kg/day IVIG, and zinc gluconate prescribed. On the third admission day, fever continued and maculopapular rashes appeared in the trunk. So, phenobarbital discontinued and echocardiography was done which was normal. On this day, the patient got tachypnea, ABG was normal and second chest CT-scan in the 4th day had the same features of the first. COVID-19 RT-PCR result was positive. On the 5th admission day, fever subsided and tachypnea improved within 4 days. After 3 days, the patient discharged with good general condition.

Discussion

In this case series study, 10 patients with COVID-19 associated PIMS who started the disease with unusual symptoms and signs like status epilepticus, appendicitis, TSS, KD and KD shock syndrome were reported. Due to the similarity with other diseases, these patients may be admitted to a ward that does not have respiratory isolation and may spread the disease to other patients and health care workers. Given that standard treatment for the disease has not been identified, this report provides our experience in management of these patients. Although children with COVID-19 are more likely to present fever and respiratory or gastrointestinal symptoms (13–15), but the most common presentation of our cases (8 cases of 10) at the time of onset was fever and rash with no respiratory symptoms, like the report of Whittaker *et al.* (7) and only 3 of our cases had cough or any other respiratory complaints. On the other hand, 2 of our patients didn't show any respiratory complaints.

However, three to four days after hospitalization, almost all patients developed respiratory symptoms like Shekerdemian *et al.*'s report (13). One of these patients had uncontrollable seizures and fever, with no other serious symptoms at the time of admission. The onset of the disease with unusual symptoms can delay the diagnosis and have irreparable consequences for the patient, or it can be confused with other diseases and management based on that disease can be performed.

The primary diagnosis of our patients were KD, TSS, prolonged febrile seizure, appendicitis, and suspected sepsis or COVID-19. In the case series reported by Whittaker *et al.* (7), the primary diagnosis was almost the same as this report, although one of our patients had prolonged febrile seizure, which could be the first report.

Sixty percent of our patients had positive laboratory evidence for COVID-19, and all of them had a history of contact. Like report of Chiotos *et al.* (15), most of them had anemia, lymphopenia, hypoalbuminemia and increased ESR and CRP (all of them). It is notable that the laboratory abnormalities may not be prominent in the admission time, but the deterioration in such measures became more sever when the general condition of the patient get worse. In two patients, PT and PTT decreased. Interestingly, regarding more severe conditions, LDH was normal in all cases in contrast to Chiotos *et al.* (15). Laboratory tests showed acute kidney injury and hepatic dysfunction in 3 and 2 patients, respectively. These findings have had different results in the studies of Verdoni *et al.* (5), Whittaker *et al.* (7), Shekerdemian *et al.* (13) and Chiotos *et al.* (15). The increase in ESR and CRP, anemia, and leukopenia were similar to our case series.

In this report, chest CT-scan was normal at the time of hospitalization in 8 patients. However, 3 days after hospitalization, like the report of Whittaker *et al.* (7), 5 patients had concurrent findings compatible with COVID-19 on chest CT-scan at the same time as the respiratory symptoms. The most common chest CT-scan findings included patchy infiltration and ground glass opacity with halo or reverse halo sign in the lower lobes of the lungs and pleural effusion. In echocardiography, ejection fraction reduced in three cases, and in two cases, ectasia and in one patient aneurysm were reported. As reported by Verdoni *et al.* (5), Whittaker *et al.* (7) and Chiotos *et al.* (15), evidence of echocardiography in some of these patients was in favor of KD, TSS, and myocarditis.

Like Whittaker *et al.* (7), Shekerdemian *et al.*'s study (13), and Chiotos *et al.* (15), almost all these patients were admitted to PICU ward. In addition to supportive care like hydration, albumin infusion, packed cell transfusion, appropriate antibiotics, and chloroquine, IVIG was given to 6 patients at a dose of 1 g/kg and in three patients at a dose of 2 g/kg. Corticosteroids were prescribed for two patients with resistant Kawasaki disease with giant aneurism and multiorgan failure. As with other studies, the prognosis of most patients was good (4, 5, 7, 13, 15). Almost all our patients discharged without complication, except one case with giant aneurysms. There was only one death in our patients, which was due to a history of uncontrolled renal failure and late referral.

Our study was the first report of PIMS in Iran. We aimed to share clinical characteristics, paraclinical findings and therapeutic experiences regarding more severe pediatric COVID-19 cases who fulfill PIMS criteria. All of them were previously healthy children, except one case with CRF.

Conclusion

Although clinical manifestations and inflammatory biomarkers in most of the children are nonspecific and milder than that in adults (16), but children with COVID-19 infection may present symptoms similar to Kawasaki disease and inflammatory syndromes. So, PIMS should be considered in patients with fever and rash, seizure, cough, tachypnea, and gastrointestinal symptoms such as vomiting, diarrhea, and abdominal pain.

Abbreviations

ABG
Arterial blood gas
CBC
Complete blood count
CDC
Center of disease control and prevention
COVID-19
(Coronavirus disease 2019)
CPK
Creatine phosphokinase
CRP
C-reactive protein
CSF

Cerebrospinal fluid
CT
Computed tomography
DVT
Deep vein thrombosis
FFP
Fresh frozen plasma
G6PDd
Glucose 6 phosphate dehydrogenase deficiency
IgG
Immunoglobulin G
IVIG
Intravenous immunoglobulin
KD
Kawasaki disease
LAD
Left anterior descending artery
LDH
Lactate dehydrogenase
LMCA
Left main coronary artery
PIMS
Pediatric inflammatory multisystem syndrome
PT
Prothrombin time
PTT
Partial thromboplastin time
RCA
Right coronary artery
RT-PCR
Real time polymerase chain reaction
SARS-CoV-2
Severe acute respiratory syndrome coronavirus 2
TSS
Toxic shock syndrome
WHO
World health organization

Declarations

Declarations

None declared

Ethics approval and consent to participate

The ethics committee of Mazandaran University of Medical Sciences approved the study protocol (No= IR.MAZUMS..REC.1398.7277). Written informed consent was obtained from parents of all patients prior to treatment.

Availability of data and material

All data generated or analyzed during this study are included in this published article.

Consent for publication

The patients of this manuscript have not been reported in any other submission by us or anyone else. Also, written informed consent was obtained from all parents of the patients prior to manuscript submission for their personal or clinical details in addition to any identifying images to be published in this study.

Competing interests

None to be declared.

Funding

None.

Authors' contributions

MS R contributed to the conception and design of the work, patients' management and supervision and revision of the study. L SH, MR N and A A drafted the manuscript. FH edited the manuscript. All authors approved the submitted version.

Acknowledgements

The authors would like to thank all patients and their parents for cooperation during treatment.

References

1. Rahimzadeh G, Ekrami Noghabi M, Kadkhodaei Elyaderani F, Navaeifar MR, Enayati AA, Manafi Anari A, et al. COVID-19 Infection in Iranian Children: A Case Series of 9 Patients. J Pediatr Rev. 2020;8(2):139–44.
2. Su L, Ma X, Yu H, Zhang Z, Bian P, Han Y, et al. The different clinical characteristics of corona virus disease cases between children and their families in China–the character of children with COVID-19. Emerg Microbes Infect. 2020;9(1):707–13.
3. Hong H, Wang Y, Chung H-T, Chen C-J. Clinical characteristics of novel coronavirus disease 2019 (COVID-19) in newborns, infants and children. Pediatr Neonatology. 2020;61(2):131–2.
4. Molloy EJ, Bearer CF. COVID-19 in children and altered inflammatory responses. Pediatr Res. 2020 Apr 3. doi:10.1038/s41390-020-0881-y.
5. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet. 2020;395(10239):1771–8.
6. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet. 2020;395(10237):1607–8.
7. Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P, et al. Clinical Characteristics of 58 Children With a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2. JAMA. 2020;e2010369. doi:10.1001/jama.2020.10369.
8. Jones VG, Mills M, Suarez D, Hogan CA, Yeh D, Segal JB, et al. COVID-19 and Kawasaki disease: novel virus and novel case. Hosp Pediatr. 2020;hpeds.2020 – 000356. doi:10.1542/hpeds.2020-000356.
9. 10.1542/hpeds.2020-000356
   Schroeder AR, Wilson KM, Ralston SL. COVID-19 and Kawasaki disease: finding the signal in the noise. Hosp Pediatr. 2020; hpeds.2020 – 000356. doi: 10.1542/hpeds.2020-000356.
10. Royal College of Paediatrics and Child Health. Guidance: paediatric multisystem inflammatory syndrome temporally associated with COVID-19. Accessed July 14. 2020. https://www.rcpch.ac.uk/resources/guidance-paediatric-multisysteminflammatory-syndrome-temporally-associatedcovid-19.
11. World Health Organization. Multisystem inflammatory syndrome in children and adolescents with COVID-19. Published May 15, 2020. Accessed July 14. 2020. https://www.who.int/publications-detail/multisystem-inflammatorysyndrome-in-children-and-adolescents-withcovid-19.
12. Centers for Disease Control and Prevention. Emergency preparedness and response: health alert network. Published July 14, 2020. Accessed May 22. 2020. https://emergency.cdc.gov/han/2020/han00432.asp.
13. Shekerdemian LS, Mahmood NR, Wolfe KK, Riggs BJ, Ross CE, McKiernan CA, et al. Characteristics and outcomes of children with coronavirus disease 2019 (COVID-19) infection admitted to US and Canadian pediatric intensive care units. JAMA Pediatr. 2020. doi:10.1001/jamapediatrics.2020.1948.
14. Qiu H, Wu J, Hong L, Luo Y, Song Q, Chen D. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. Lancet Infect Dis. 2020;20:689–96.
15. Chiotos K, Bassiri H, Behrens EM, Blatz AM, Chang J, Diorio C, et al. Multisystem Inflammatory Syndrome in Children during the COVID-19 pandemic: a case series. J Ped Infect Dis Soc. 2020;9(3):393–8.
16. Bai K, Liu W, Liu C, Fu Y, Hu J, Qin Y, et al. Clinical Analysis of 25 COVID-19 Infections in Children. Ped Infect Dis. 2020;39(7):e100-e3.