Clinical Case Reports International

Case Presentation
Published: 21 Dec, 2021

Cardiogenic Shock Associated with PIMS-TS- *De Novo* Myocardial Involvement or Subacute COVID-19-Myocarditis? Discussions Around a Case Report and Literature Review

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Abstract

We describe a case of Pediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2 (PIMS-TS) in a 6-year-old boy, who developed signs and symptoms of cardiogenic shock in an early stage. The echocardiography revealed severe systolic dysfunction, mild pleural and pericardial effusion, and coronary artery dilation. The patient developed multiorgan dysfunction and received treatment with intravenous immunoglobulin, Interleukin-1 receptor antagonist, and high doses of corticosteroids, vasoactive and inotropic support, anticoagulant therapy, and diuretics with complete resolution of clinical heart failure and normalized Left Ventricle (LV) ejection fraction within 10 days. Further studies are necessary to know if a better prognosis in PIMS-TS related severe myocarditis is expected in patients with previously normal myocardium compared with patients with myocardial damage in acute phase of SARS-CoV-2 infection through direct injury of the virus (non-immune mechanism).

Keywords: COVID-19; Infection; Children; PIMS-TS; Cardiogenic shock; Treatment; Kawasaki Disease Shock Syndrome

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Received Date: *25 Nov 2021*
Accepted Date: *14 Dec 2021*
Published Date: *21 Dec 2021*

Citation:
Ionescu MD, Filip C, Marin LI, Gavriliu LC, Stefan MC, Balgradean M. Cardiogenic Shock Associated with PIMS-TS- De Novo Myocardial Involvement or Subacute COVID-19-Myocarditis? Discussions Around a Case Report and Literature Review. Clin Case Rep Int. 2021; 5: 1253.

Introduction

Multisystem Inflammatory Syndrome in Children (MIS-C) is the name provided by the Centers for Disease Control and Prevention (CDC). The proposed definition implies the demonstration of association with SARS-CoV-2 infection by RT-PCR, antigen test, serology, or COVID-19 exposure within 4 weeks before the onset of symptoms, in an individual aged <21 years presenting with fever, inflammation, evidence of multisystem (≥ 2) organ involvement and no alternative plausible diagnoses. Pediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2 infection (PIMS-TS) is the name provided by Royal College of Pediatrics and Child Health (RCPCH), and refers to a child presenting with persistent fever, inflammation, evidence of single or multiorgan dysfunction, with no evidence of a microbial cause and with a positive or negative SARS-CoV-2 PCR test [1-3]. It was initially thought that children were asymptomatic or mildly symptomatic in SARS-CoV-2 infection, however 4,404 patients with PIMS-TS were reported by CDC this year. Half of the children with PIMS-TS were between the ages of 5 and 13 years. 99% of patients had a positive test result for SARS-CoV-2 and 1% had contact with someone with COVID-19 [4].

The clinical features of PIMS-TS patients are non-specific and wide; the most common signs and symptoms are: Persistent fever, hands and feet edema, conjunctivitis, swollen and cracked red lips, rash, abdominal pain, vomiting, diarrhea, shock, and lymphadenopathy [5,6]. Godfred-Cato et al. [7] studied the characteristics of 570 patients with PIMS-TS and reported the following system involvement: Gastrointestinal 90.9%, cardiovascular 86.5%, dermatologic 70.9%, hematologic 73.9%, respiratory 63.0%, neurologic 38.2% and renal 18.4%. The most common cardiovascular findings were hypotension 49.5%, elevated NT-pro-BNP 43.2%, cardiac dysfunction 40.6%, shock 35.4%, elevated troponin 30.9%, mitral regurgitation 25.5%, pericardial effusion 23.9%, myocarditis

Table 1: Investigations at the time of admission.

Parameter	Patient	Reference values
Complete Blood Count (CBC)		
White blood cells count-WBC (× 10^3 µL)	25.3	5.00-14.50
Neutrophils-NEU (× 10^3 µL)	22.83	1.50-8
Lymphocytes-LYM (× 10^3 µL)	1.95	1.50-7
Platelets-PLT (× 10^3/µL)	106	150.00-450.00
Hemoglobin-HGB (g/dL)	10	11.50-14.50
Mean corpuscular volume-MCV (fL)	76.3	75-89
Inflammatory markers		
C-Reactive Protein-CRP (mg/L)	137.92	00.00-5.00
Procalcitonin-PCT (ng/mL)	1.92	<0.05
Interleukin 6-IL-6 (pg/mL)	40.36	<7
Fibrinogen (mg/dL)	364	140.00-360.00
Acid-Base balance		
pH	7.413	7.35-7.45
PCO2 (mmHg)	47	32-48
HCO3 (mmol/L)	29.3	22-26
Electrolytes		
Na (mmol/L)	136.6	138-144
K (mmol/L)	3.44	3.4-4.9
Biochemistry		
TGO (U/L)	59	2.00-48.00
TGP (U/L)	32	2.00-29.00
Urea (mg/dL)	43	<39
Creatinine (mg/dL)	0.9	<1.2
Total seric protein (g/dL)	5.32	6.00-8.00
Albumin (g/dL)	2.81	3.80-5.40
LDH (UI/L)	288	120.00-300.00
CK (U/L)	26	7.00-149.00
CK-MB (U/L)	23	7.00-25.00
Troponin T (ng/L)	<40	<40
NT-pro-BNP (pg/mL)	48793	<125
APTT (sec)	28.2	24.00-37.00
D-Dimer (µg/mL)	7	0.00-0.50
PT (sec)	13.1	11.30-15.60
INR	0.96	0.84-1.20
Ferritin (ng/mL)	542.3	14-124
Bacteriology		
Blood culture	Negative	
Urine culture	Negative	
Stool culture	Negative	
Serology		
SARS-CoV-2 IgG	POSITIVE	
RT-PCR SARS-CoV-2	Negative	

22.8%, coronary artery dilatation 18.6% and congestive heart failure 7% [7].

As a new described syndrome, first reported on April 7th, 2020 [1], PIMS-TS was initially considered Kawasaki Disease (KD)-like syndrome due to persistent fever, rash, cervical lymphadenopathy, ocular and oral mucosal changes, peripheral extremity changes such as erythema of palms, edema of hands and feet, and elevated inflammatory markers. PIMS-TS are usually associated with an incomplete form of KD. The age of onset is mostly >5-year-old in PIMS-TS and <5-year-old in KD. Patients with Kawasaki disease and poor myocardial function may present with severe systolic dysfunction or shock, which defines Kawasaki Disease Shock Syndrome (KDSS), a potentially life-threatening condition [8].

Shock, as a cardiovascular complication and modality of onset may be present in more than one third of the children [9]. Shock accompanying PIMS-TS may be cardiogenic, distributive or both [10,11]. To increase the degree of recognition of the severe cardiovascular involvement, we selected a PIMS-TS case from the Department of Pediatrics of Marie Curie Children's Emergency Hospital, Bucharest, Romania.

Case Presentation

A six-year-old male child was admitted to our pediatric department by transfer from another hospital, where he was admitted with a five-day history of high fever (39°C to 40°C), headache, apathy, and gastrointestinal symptoms (diffuse abdominal pain and vomit). During the first 24 h, he became drowsy, developed edema of the hands and feet, and hypotension. Despite fluid resuscitation with normal saline and inotropic agents, the patient's blood pressure remained low at 63 mmHg/23 mmHg and he was transferred to our pediatric ward for further investigation and treatment. Previously, he was a healthy child with no past medical history. The family also revealed that a SARS-CoV-2 outbreak was present in the kindergarten two months ago. The COVID-19 exposure matches the peak incidence of SARS-CoV-2 third wave (middle March 2021) in Romania (Figure 1).

The physical examination on admission showed pale, dry skin, palpebral and palmoplantar edema, red and cracked lips, conjunctival erythema, cervical lymphadenopathy, decreased skin turgor, capillary refill time (CRT<3 sec), oliguria. He had tachypnea (respiratory rate =50 breaths per minute), dyspnea and orthopnea, chest retractions, diminished breath sounds in both lung bases, fine crackles, 92% Oxygen Saturation (SpO2) on room air. The cardiovascular assessment showed tachycardia, (heart rate =120 beats per minute), Blood Pressure (BP) 65/47 mmHg and muffled heart sounds. The liver edge was palpable 3 cm under the ribs. The child was drowsy, Glasgow Coma Scale (GCS=12). His weight on admission was 17.5 kg, which represented a 2-kilogram weight gain.

Laboratory findings at the time of admission are shown in Table 1. Electrocardiogram (ECG) in evolution showed ST-T changes- mild

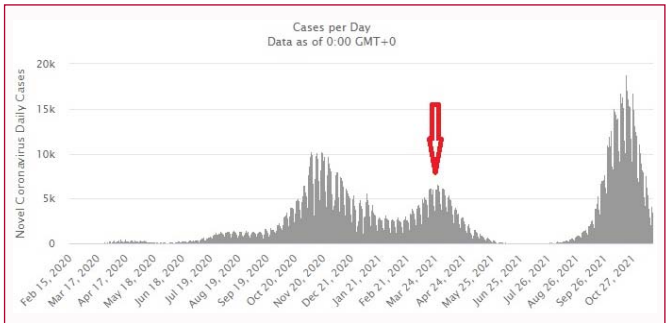


Figure 1: Daily new cases in Romania (February 15th 2020 to November 18th 2021).

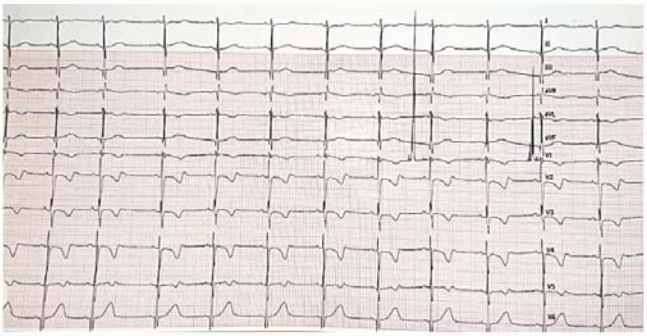


Figure 2: Electrocardiogram findings.

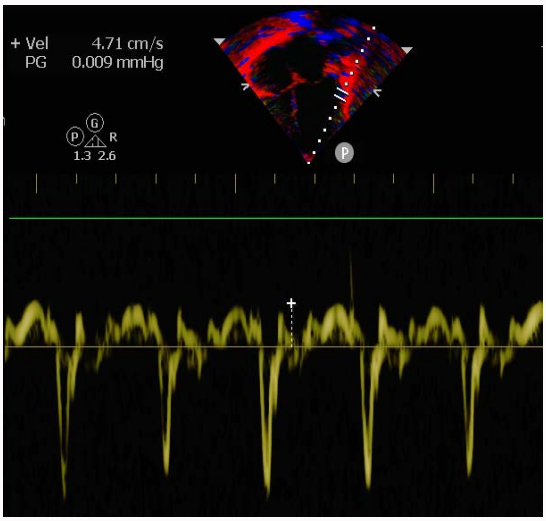


Figure 3: Coronary involvement (RCA and LCA Z score).

ST depression in V2-V4 and negative/biphasic T waves in V1-V5, aVL (Figure 2).

Considering the clinical presentation with cardiogenic shock, an echocardiography was performed in emergency and it revealed severe systolic LV dysfunction with diffuse ventricular hypokinesia (LV ejection fraction-25%), mild RV dysfunction, small pleural and pericardial effusion, mild coronary artery dilation (right coronary artery- RCA-Z score +2,05 and left coronary artery- LCA-Z score +2,2) (Figure 3, 4).

All the criteria for the definition of PIMS-TS according to RCPCH, CDC and WHO were fulfilled: Child's age <19 years, fever lasting for more than 3 days, mucocutaneous inflammation signs, gastrointestinal symptoms, hypotension, features of myocardial dysfunction (muffled heart sounds, elevated NT-pro-BNP, severe systolic dysfunction and coronary abnormalities), evidence of coagulopathy (increased D-dimers), elevated markers of inflammation, no obvious microbial cause for inflammation, positive serology for SARS-CoV-2 infection (Table 2).

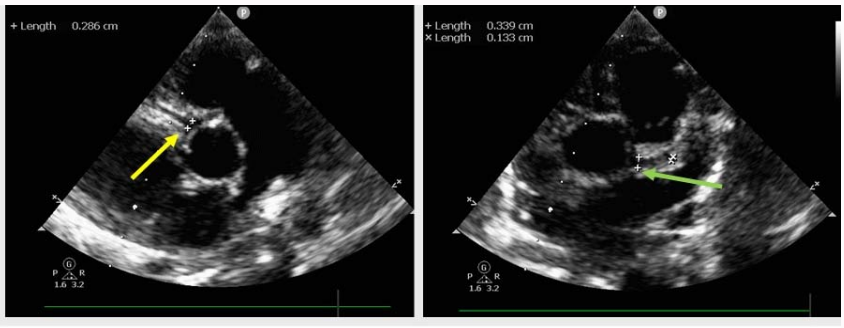
The case was approached by a multidisciplinary team involving a pediatrician, an infectious disease specialist, a pediatric cardiologist, a radiologist, and an intensive care physician. It was considered PIMS-TS with cardiogenic shock, similar to KDSS.

It was treated with: Intravenous Immunoglobulin (IVIG) 500 mg/kg for 5 days, Interleukin-1 receptor antagonist 2 mg/kg for 7 days, high doses of corticosteroids (Methylprednisolone 4 mg/kg), antibiotic therapy (Meropenem in association with Vancomycin), All the criteria for the definition of PIMS-TS according to RCPCH, CDC and WHO were fulfilled: Child's age <19 years, fever lasting for more than 3 days, oxygen therapy, anticoagulant (Enoxaparin 100 UI/kg/day), vasoactive and inotropic support, Adrenaline (initially dosage 0.1 µg/kg/min, then in decreasing dosage until minimum 0.02 µg/kg/min) and Dopamine (10 µg/kg/min) for five days, subsequently, he received treatment with combined diuretic therapy, ACE - inhibitor and beta-blocker.

The clinical evolution following the treatment was favorable, with the improvement of general condition and the resolution of heart failure signs and symptoms. The cardiac ultrasound showed an increase of the left ventricular ejection fraction to 60% and normal aspect of the coronary arteries at 10 days from admission in our clinic.

CBC showed a normal number of leukocytes after 10 days of treatment. The inflammatory response slowly decreased with normalization of the values in 5 days (Figure 5).

The patient was discharged after 18 days of hospitalization and received treatment with Aspirin, Bisoprolol, Lisinopril, Spironolactone (cardiac remodeling). A cardiac ultrasound was



Right coronary artery	Dimension	Z score
Right coronary artery-origin	2,8 mm	2,05

Left coronary artery	Dimension	Z score
Left coronary artery-origin	3,4 mm	2,2
Circumflex artery	1,3 mm	-1,1
Left anterior descending artery	2,1 mm	0,75

Figure 4: Systolic dysfunction.

Table 2: Case definition of PIMS-TS/MIS-C according to CDC [3], RCPCH [2], WHO [12].

Multisystem Inflammatory Syndrome in Children (MIS-C) CDC - Case definition	Pediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS-TS) RCPCH-Case definition	Multisystem Inflammatory Syndrome in Children (MIS-C) WHO - Case definition	Case presentation
Age <21 years		Age 0-19 years	Age
Fever >38.0°C for ≥ 24 hours	Persistent fever >38.5°C	Fever ≥ 3 Days	Fever
Inflammation			
• CRP, ESR, Procalcitonin	1. Neutroplilia	1. ESR	• CRP
• Fibrinogen	2. Elevated CRP	2. CRP	• Procalcitonin
• D-dimer	3. Lymphopenia	3. Procalcitonin	• Fibrinogen
• Ferritin			• D-dimer
• LDH			• Ferritin
• IL-6 level			• IL-6 level
• Neutroplilia			• Neutroplilia
• Lymphocytopenia			• Hypoalbuminemia
• Hypoalbuminemia			
Multisystem (>2) organ involvement	**Evidence of single or multi-organ dysfunction**	**At least 2 of the following:**	**Multisystem organ involvement**
• Cardiac	1. Shock	1. Rash, bilateral non-purulent conjunctivitis or mucocutaneous inflammation signs (oral, hands or feet).	**Cardiac:**
• Renal	2. Cardiac	2. Hypotension or shock	• Hypotension
• Respiratory	3. Respiratory	3. Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/NT-pro-BNP)	• Systolic dysfunction
• Hematologic	4. Renal	4. Evidence of coagulopathy (PT, PTT, elevated D-Dimers)	• Cardiogenic shock
• Dermatologic	5. Gastrointestinal	5. Acute gastrointestinal symptoms	• Pericardial effusion
• Neurological	6. Neurological disorder		• Coronary artery dilation
			Hematologic/Coagulopathy:
			• Elevated D-dimer
			Gastrointestinal:
			• Acute gastrointestinal symptoms
			Dermatologic:
			• Palpebral and palmoplantar edema, red and cracked lips, conjunctional erythema
AND	**AND**	**AND**	
No alternative plausible diagnoses	Exclusion of any other microbial cause	No other obvious microbial cause	No other microbial cause
AND	**AND**	**AND**	
• Positives SARS-CoV-2 infection by RT-PCR,	SARS-CoV-2 PCR testing may be positive or negative	• Positives SARS-CoV-2 infection by RT-PCR,	Positives SARS-CoV-2 serology
• Serology		• Serology	
• Antigen test		• Antigen test	
• COVID-19 exposure within the 4 weeks prior to the onset of symptoms		• COVID-19 exposure within the 4 weeks prior to the onset of symptoms	

performed a month later, showing normal heart function, allowing the gradually withdrawal of the treatment.

Discussion

On April 7th, 2020, the first PIMS case report was published [13], and since then several case reports or case series outlined the importance of PIMS as a life-threatening condition. There are three types of syndromes described as clinical phenotypes that can occur at the onset of PIMS: 1) Fever with hyperinflammation, 2) Kawasaki disease-like features, and 3) Shock [14]. PIMS-related shock is a frequent clinical presentation described either as vasoplegic (warm) shock unresponsive to fluid resuscitation [15], cardiogenic, or a combination of them [9]. Cardiogenic shock is an acute state with low cardiac output which furthermore leads to hypoperfusion and

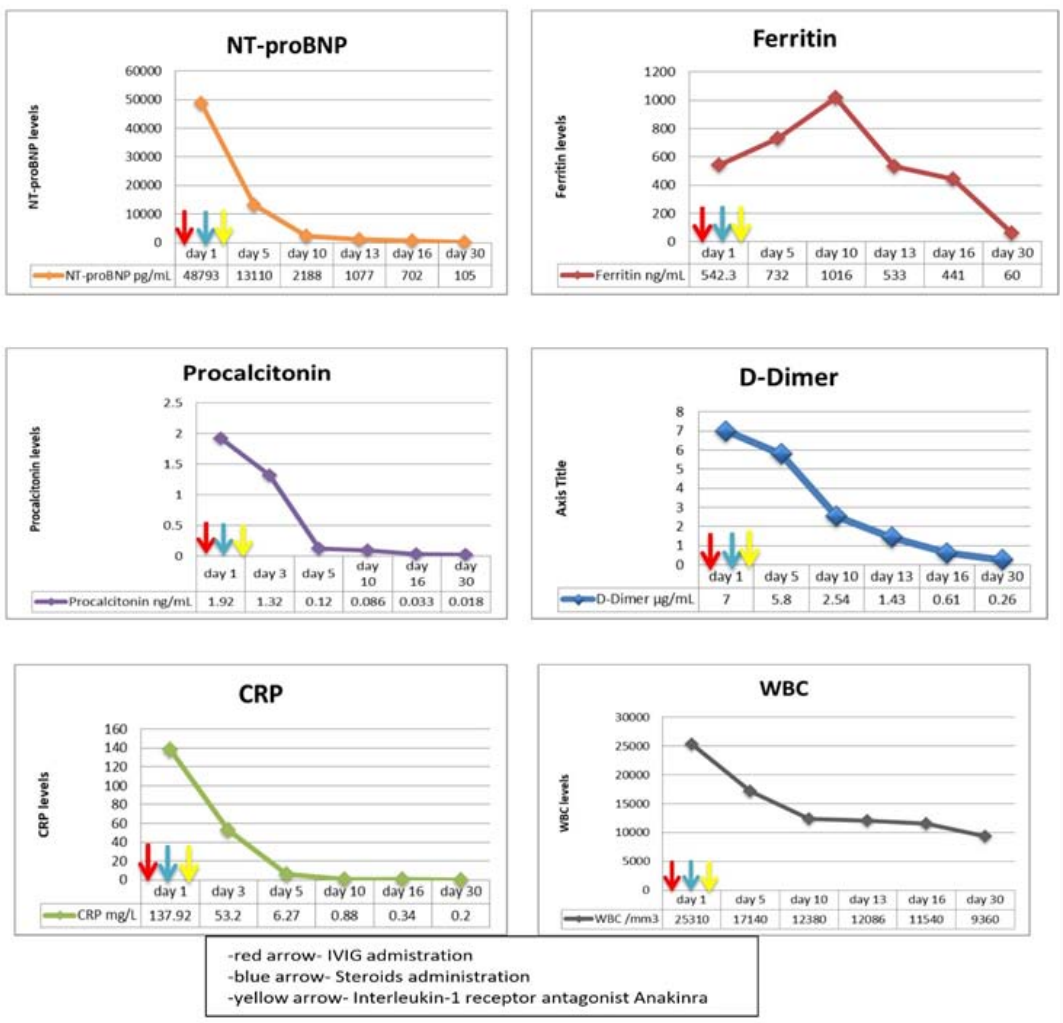


Figure 5: The dynamics of biomarkers during admission.

tissue hypoxia [16]. The pathophysiology of PIMS related cardiogenic shock is not fully understood. In the symptomatic phase, three main immune mechanisms have an impact on cardiovascular involvement: the appearance of a cytokine storm, activation of immune cells (including neutrophils), and deposits of immune complexes. The cytokine storm is mainly responsible for vasoplegia while IL6, CRP and activation of neutrophils lead to myocardial injury [17]. A similar condition to PIMS related shock state is Kawasaki disease - shock syndrome, first described by Kanegaye et al. [8]. However, Kawasaki disease was first described in the 1960s [18] so during the five decades since it was reported, its pathogeny was better studied. Because of clinical similarities between PIMS and Kawasaki disease, it has been assumed that PIMS might be an immune complex-induced vasculitis and there might be several common pathways between Kawasaki disease and PIMS [19].

Myocarditis (described in several degrees, usually subclinical/mild) is a constant finding in almost all patients at the onset of Kawasaki disease, before the appearance of coronary aneurysms. Several studies reveal myocardial inflammation at the microscopic examination as part of postmortem examination [20], on endomyocardial biopsy [21], or cardiac MRI. Moreover, Printz et al. [22] indicate an association between the level of systemic inflammatory status in Kawasaki disease and the left ventricle ejection fraction.

The endomyocardial biopsy cannot be routinely practiced, being an invasive procedure. Due to lack of consensus for the diagnosis of myocarditis, we defined myocarditis based on the criteria mentioned by Dasgupta et al. [23]: Elevated cardiac enzymes, ST segment elevation or depression on ECG, regional/global wall motion abnormalities with impaired LV function on echocardiography.

NT-pro-BNP is a polypeptide produced in atrial and left ventricle myocardiocytes when they are prone to mechanical stretch [24]. Therefore, NT-pro-BNP is a well-known biomarker for heart failure.

We hypothesize 2 possible theories. Firstly, myocarditis might have been initiated due to SARS-CoV-2 infection. It overlaps the 3rd wave of the SARS-CoV-2 outbreak in Romania and the child was asymptomatic. Several studies indicate that subclinical myocarditis can occur in pediatric patients during viral infections [25,26]. Symptoms of heart failure appeared after a 1.5 month delay from the initial infection. Therefore, an underlying mild degree of myocardial edema might persist after the initial SARS-CoV-2 infection. It might have been in resolution (activation of myocardial fibroblasts) if PIMS-TS would not have occurred. Due to PIMS-TS, a huge amount of vasoactive cytokines were released, leading to vasoplegic shock and increasing the level of myocardial edema which might explain the pathophysiology of cardiogenic shock in this patient. Troponin level

was in the normal range at the moment of admission in contrast to a marked elevated level of NT-pro-BNP. Due to these two processes that overlapped (subclinical myocarditis and the cytokine storm which increased the level of interstitial edema of the heart) the myocardiocytes were increasingly stretched but not injured, leading to extremely high levels of NT-pro-BNP while the levels of troponin were at the upper limit of normal range values.

The second hypothesis refers to a newly developed PIMS-TS intramyocardial edema in a patient without myocardial damage during the acute phase of SARS-CoV-2 infection [27,28]. Like we mentioned before, three main mechanisms are involved in PIMS-TS development, according to which pathway is more prominent, so it can clinically present as fulminant myocarditis (mostly described in adults), acute heart failure, or mild/moderate myocardial enzyme elevation [29]. Acute heart failure manifestation is linked with the over stimulating vasoactive cytokine pathway which furthermore leads to vasoplegic shock. Myocardial cell injury might have happened if the 2nd pathway would have been more prominent (activation of immune cells, neutrophils included) together with increased levels of IL6 and CRP. In this case, the levels of IL6 are CRP was mildly elevated, not leading to an acute muscular cardiac destruction. Once newly developed intramyocardial edema and distributive shock can lead to low LV ejection fraction and clinical manifestation of shock. So we admit that the shock in our case had two components: Cardiogenic and vasoplegic.

The cardiogenic shock had a favorable outcome in our case using 2 inotropic agents Adrenaline (initially dosage 0.1 μg/kg/min,) and Dopamine (10 μg/kg/min) for five days, then only Dopamine for another five days alongside with cardiac remodeling medication: Angiotensin-Converting Enzyme Inhibitor (Lisinopril), Spironolactone, Furosemide and Bisoprolol [27]. Clinical condition progressively improved, with resolution of pulmonary stasis, good cerebral perfusion and normalized blood pressure values within 7 days, with no mechanical circulatory support required. This clinical presentation matches the information reported by several authors [17,28,29], in which patients with PIMS-TS- cardiogenic shock had a favorable outcome primarily due to immune-mediated damage rather than myocardial injury post SARS-CoV-2 replication. The full recovery in such a short time (with normalized cardiac function by echocardiography in 10 days) using corticosteroids, IVIG, IL-1 receptor antagonist and supportive cardiac medication could be an argument for our second hypothesis consisting with PIMS-TS related myocarditis on previously normal myocardium.

Conclusion

PIMS-TS is a new described pediatric syndrome which can present as several clinical phenotypes, and some of them can be life-threatening. Cardiogenic shock related to PIMS-TS (with underlying immune myocarditis) is an often clinical presentation with favorable outcome if specific treatment against cytokine storm and supportive cardiac medication are promptly administered. Further studies are necessary to know if a better prognosis in PIMS-TS related severe myocarditis is expected in patients with previously normal myocardium compared with patients with myocardial damage in acute phase of SARS-CoV-2 infection through direct injury of the virus (non-immune mechanism).

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