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Case report: Pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 with severe myocardial dysfunction. Is there any hope in immunotherapy?

Julita Tokarek

Medical University of Lodz

https://orcid.org/0000-0003-4527-3355

Emilian Budny

Medical University of Lodz

https://orcid.org/0009-0006-7737-5689

Renata Szmigielska

Medical University of Lodz

https://orcid.org/0000-0002-3528-6139

Abstract

Pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) develops in a small percentage of children after COVID-19, however, it might cause severe myocardial dysfunction. The pathogenesis of this disease includes systemic hyper-inflammation with cytokine storm. This case report concerns a 12-year-old boy with PIMS-TS who presented severe respiratory and circulatory failure with increased inflammatory markers and significant reduction of left ventricle ejaculatory fraction (LVEF) from 65% to 35%. The recommended therapy with the use of vasopressors, corticosteroids, intravenous immunoglobulins and mechanical ventilation was introduced and his condition gradually improved. However, after few days, aggravation of cardiac symptoms occurred again and among other treatment, the therapy with the use of anakinra - the human interleukin 1 receptor antagonist protein was introduced. This case highlights a satisfactory regression of cardiac disturbances and generally favorable outcome of the treatment in patients with PIMS-TS with the use of immunomodulatory therapy.

Keywords: COVID-19, PIMS-TS, anakinra, immunomodulatory therapy

1. Introduction

Pediatric inflammatory multisystem syndrome (PIMS) temporally associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also known as multisystem inflammatory syndrome in children (MIS-C), is a relatively new disease that develops in a small percentage of children after COVID-19. Main symptoms of PIMS-TS include high fever, gastrointestinal upset, neurological disturbances, cardiac complications and it might even lead to a multiorgan dysfunction [1]. This syndrome is characterized by systemic hyper-inflammation with development of cytokine storm, mainly involving interleukin 1 (IL-1) and interleukin 6 (IL-6) [2].

2. Case report

A 12-year-old boy was admitted to the hospital to the Cardiology and Rheumatology Department with fever (up to 39°C), sore throat, dizziness accompanied by headache and vomiting for past three days. Five days prior to admission he ended quarantine because of a contact with a patient with COVID-19. Laboratory tests revealed significantly elevated levels of anti-SARS-CoV-2 antibodies, both IgM (3.11 Index) and IgG (1140 BAU/ml), which proved a recent COVID-19 infection. On the day of admission, the reverse transcription polymerase chain reaction (RT-PCR) test for COVID-19 was negative. The inflammatory markers: C-reactive protein (CRP) and procalcitonin (PCT), along with N-terminal prohormone of brain natriuretic peptide (NT-proBNP) were highly increased (CRP 248.2 mg/l, PCT 10.88 ng/ml, NT-proBNP 7469 pg/ml). Moreover, disturbances in the coagulation profile with thrombocytopenia were present. The chest X-ray revealed the densities dependent on inflammatory changes in both lungs. Therefore, the diagnosis of pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) was stated and treatment in accordance with the then guidelines was introduced.

Although the echocardiography on the day of admission presented normal anatomy and function of myocardium with the left ventricle ejection fraction (LVEF) of 65%, the exacerbation of respiratory and circulatory failure occurred on the next day the and the patient was admitted to the Intensive Care Unit (ICU). His condition was severe, he showed increased respiratory effort on passive oxygen therapy, with blood pressure (BP) of 70/40 mmHg and heart rate (HR) 134/min. The high flow Airvo™ 2 oxygen therapy was introduced, however, on the following day, he presented increasing respiratory effort and dyspnea with symptoms of pulmonary edema and was intubated. He received intravenous antibiotic therapy (ceftriaxone, clindamycin and voriconazole), anticoagulants, parenteral nutrition and intensive fluid therapy.

The developing circulatory failure was treated with the infusion of norepinephrine, pentoxifylline, solumedrol (2 mg/kg) and intravenous immunoglobulins (IVIG) (2 g/kg). The echocardiography showed the presence of hypokinesis and LVEF lowered to 35%. Moreover, NT-proBNP increased up to 33812 pg/ml. Due to this deterioration, this case was consulted with the Cardiosurgery Department for the potential use of extracorporeal membrane oxygenation (ECMO). However, after the infusion of dobutamine, levosimendan and magnesium sulfate, intensification of diuretic therapy, modification of ventilation parameters, and prone positioning, the boy's condition gradually improved. After returning to the supine position, the control chest X-ray was taken and showed left-sided pneumothorax and pneumomediastinum and therefore, left-sided pleural drainage was inserted for two days. Subsequently, the LVEF reached 57% and he was extubated after nine days in total and passive oxygen therapy was introduced.

However, on the 13th day of hospitalization, the symptoms of circulatory failure occurred again, which included tachycardia, abnormalities in electrocardiography (prolonged QRS duration), hypokinesis and LVEF of 44%. The laboratory test showed increased high sensitive Troponin I (hsTnI) to 1.403 ng/ml and NT-proBNP of 12307 pg/ml. The cardiologists suspected the diagnosis of takotsubo cardiomyopathy. Despite this deterioration, the patient showed no signs of respiratory failure and required no respiratory support. Due to the severe condition of the patient and aggravation of cardiac symptoms, levosimendan (six days after the withdrawal), norepinephrine and IVIG (2x 0.5 g/kg) were introduced again. Furthermore, after consultation with rheumatologists and National Consultant for Pediatrics, alongside with his mother's consent, the patient received the immunosuppressive biological therapy (anakinra - the human interleukin 1 (IL-1) receptor antagonist protein [2]).

During next days, a gradual improvement of patient's condition was noticed (better contractility of the myocardium, increase of LVEF up to 68%). The most important changes in laboratory test and echocardiography during the whole hospitalization are presented in Table 1. Despite the improvement of the patient's cardiopulmonary condition, he presented features of advanced myopathy and required intensive and systematic motor rehabilitation, which brought gradual results. After 33 days of hospitalization, the patient was discharged from ICU, presenting full cardiovascular and respiratory efficiency and was referred for further treatment and rehabilitation to the Cardiology and Rheumatology Department.

Table 1. The most important changes in laboratory test and echocardiography during hospitalization.

Day of hospitalization / Parameter	1.	2.	8.	13.	16.	18.	20.	25.	30.
CRP [mg/l]	248.2	317.8	19.6	10.1	4.6	1.8	1.1	0.4	1.5
PCT [ng/ml]	10.88	12.36	0.26	0.12	0.25	0.15	0.09	0.02	0.06
hsTnI [ng/ml]		0.302	0.636	1.403	1.155	0.933	0.629	0.215	0.099
NT-pro BNP [pg/ml]	7469	33812	675.7	12307	33895	21042	13519		
LVEF [%]	65	35	57	44	45	50	55	68	61

3. Discussion

Pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) might manifest with different signs and symptoms, ranging from fever and inflammation to shock, myocardial injury, and even development of coronary artery aneurysms [3]. PIMS-TS develops in 0,1% children after predominantly mild or symptomless COVID-19 infection [4]. Cardiac disturbances are found in a high proportion of these patients [5]. Mortality despite treatment is estimated at 1.5-2% [6]. Current recommendations based on expert consensus include the use of cardiac support, corticosteroids, intravenous immunoglobulins (IVIG) and immunomodulatory agents in treatment of this syndrome [5].

Due to the fact that the cytokine storm is frequently used as an explanation and cause of the observed disorders [7], the use of immunosuppressive therapy appears to be effective, mostly in advanced stages of the disease [8], [9]. Anakinra is one of the treatment options as an immunomodulatory agent that acts as the human interleukin 1 (IL-1) receptor antagonist [2]. Although the immunomodulatory therapy with the use of anakinra is recommended in this syndrome, this remains as an off-label application. The usage of anakinra in the pediatric population with PIMS-TS has been reported in the literature [10], [11] and these reports were the basis for the use of this treatment in described case. As an IL-1 receptor antagonist, it can suppress an excessive immune response, inhibit the cytokine storm and therefore, restore homeostasis in immune system and alleviate the symptoms of the disease. The studies have shown that the immunomodulatory approach treatment in PIMS-TS patients with myocardial dysfunction might result in a faster recovery [12]. Moreover, anakinra combined with subsequent IVIG and corticosteroids demonstrated to be effective in restoring a normal LVEF, especially for patients in severe condition, not responding to standard treatment [12].

4. Conclusion

Pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 might cause a multiorgan failure with severe myocardial dysfunction, and even lead to complications such as takotsubo cardiomyopathy. Despite advanced myocardial hypokinesis and significant reduction of LVEF, proper treatment with the use of vasopressors, corticosteroids, intravenous immunoglobulins and in some cases, immunosuppressive biological therapy (e.g. anakinra) might result in a satisfactory regression of changes and generally favorable outcome of the treatment.

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