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CASE REPORT

The challenges of multisystem inflammatory syndrome diagnosis and treatment

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Abstract

A two-year-old girl with fever, diarrhea and vomiting was presented to the Emergency Department (ED). A maculopapular rash on the face, cervical lymphadenopathy and 1st degree dehydration were being noted. Laboratory results showed leukocytosis, neutrophilia and a high level of C-reactive protein (CRP). Amoxicillin was prescribed, but the patient's state did not improve. She returned to ED with rash all over her body and 2nd degree dehydration. Laboratory results revealed thrombocytopenia and a more increased level of CRP. It was found that her mother has been diagnosed with the coronavirus disease approximately two months ago. Extended laboratory results showed signs of mild anemia, increased levels of liver enzymes, procalcitonin, troponin, N-terminal prohormone of brain natriuretic peptide, D-dimers, ferritin. Anti-SARS-CoV-2 (severe acute respiratory syndrome-coronavirus) IgG (immunoglobulin G) were detected. Multisystem inflammatory syndrome was diagnosed. Pediatric echocardiography revealed 10 mm of fluids in pericardium, I degree mitral valve regurgitation, dilated left coronary artery. She was given a treatment with intravenous Immunoglobulin G, methylprednisolone and aspirin, but her state did not improve. A treatment with Tocilizumab was given, but it did not have a much more positive effect, laboratory results showed progressed leucocytosis and neutrophilia. As the last resort, biology treatment with a recombinant form of human interleukin-1 receptor antagonist Anakinra was started and after a week all symptoms changed, and laboratory results regressed.

Keywords

Multisystem inflammatory syndrome; Coronavirus; Prolonged fever; Dilated coronary artery

1. Introduction

Coronavirus disease (SARS-CoV-2) originated at Wuhan city, China at the end of 2019 and rapidly spread across the whole world [1]. This disease is caused by severe acute respiratory syndrome coronavirus 2 and usually has clinical features similar to influenza [2]. Children often have mild gastrointestinal or respiratory symptoms of SARS-CoV-2 [3].

Multisystem inflammatory syndrome in children (MIS-C) is a rare complication which sometimes develops after SARS-CoV-2 infection [4]. Even though the incident of this syndrome is uncommon, it is important to make the accurate diagnosis to prescribe such a needed treatment on time. MIS-C has polymorphous clinical features, which makes a diagnosis sometimes really challenging [5].

In this Case Report from Hospital of Lithuanian University of Health Sciences Kaunas Clinics, we are going to present a clinical case involving a two-year-old girl with prolonged high-grade fever and symptoms of acute abdomen in order to increase knowledge on this topic, especially difficult diagnosis and treatment of MIS-C.

2. Clinical case

A two-year-old girl with high-grade fever and symptoms of acute abdomen was presented to the Emergency Department (ED). Fever has started three days ago, with the temperature rising up till 40 °C every five hours.

On physical examination, she was alert and oriented. Her vital signs were as follows: temperature: 38.8 °C, heart rate: 120 beats/min, blood pressure: 100/60 mmHg, respiratory rate: 30/min. Her height and weight were at the 50th percentile. There was a maculopapular rash on the face. Also, swollen tonsils and cervical lymphadenopathy and signs of 1st degree dehydration were being notified. Lungs were clear to auscultation. There were no painful areas of the abdomen, but she was vomiting and had frequent loose, watery stools. The rest of the examination findings were unremarkable.

Initial laboratory evaluations showed leukocytosis (19 $\times$ 10^9/L, reference range 5–12 $\times$ 10^9/L), neutrophilia (14.7 $\times$

10^9/L, reference range 1.6–8.3 × 10^9/L), high level of CRP (93.9 mg/L, reference range 0–5 mg/L).

Based on the physical examination such as swollen tonsils and cervical lymphadenopathy as well as laboratory findings, the patient was being diagnosed with tonsillitis and Amoxicillin for 10 days was prescribed.

Unfortunately, the patient's state did not improve. She no longer had diarrhea or vomiting, but the fever remained persistent, and the girl was not eating properly and was not drinking enough fluids. Therefore, after two days, she was presented to the ED once again.

On physical examination, she was noted as fatigued and dizzy. Her vital signs were as follows: temperature: 39 °C, heart rate: 138 beats/min, blood pressure: 90/60 mmHg, respiratory rate: 40/min. Rash on the skin covered the whole body. There were signs of 2nd degree dehydration. Other examination findings remained the same.

Laboratory evaluation revealed the following: leucocytosis and neutrophilia remained, but there were also fewer thrombocytes (155 × 10^9/L, reference range 200–582 × 10^9/L). CRP level was increased significantly (199.8 mg/L). No signs of viral or bacterial infection were found as virological tests for sixteen types of viruses such as influenza, Epstein-Barr were negative and blood, urine and fecal cultures results were also negative. Chest X-ray showed no signs of inflammation.

Unfortunately, the patient's state did not improve much. After further questioning, it was found out that her mother had been diagnosed with the coronavirus disease approximately two months ago. She was being hospitalized at the Pediatric Department (PD).

More laboratory tests were performed (Table 1). Laboratory evaluations showed signs of mild anemia, leukocytosis, neutrophilia, thrombocytopenia, increased levels of liver enzymes, procalcitonin, CRP, troponin, N-terminal prohormone of brain natriuretic peptide, D-dimers, ferritin. Also, an antibody test for the coronavirus disease was performed and a higher level of IgG has been detected.

3. Final diagnosis

Multisystem inflammatory syndrome.

4. Hospital course

A pediatric cardiologist was consulted for further evaluation. Echocardiography revealed 10 mm of fluids in pericardium, 1st degree mitral valve regurgitation as well as dilated left coronary artery (Fig. 1). The function of the heart was not affected.

Before MIS-C was diagnosed, the patient has received empiric antibacterial treatment with amoxicillin until negative result of blood and urine cultures, although it was changed due to no positive changes in the patient's state to sultamicillin and clarithromycin assuming it would have a better result on treating the patient as this combination of antibiotics have a wider spectrum for various bacteria, including atypical pathogens such as Chlamydia pneumoniae and Mycoplasma pneumoniae.

The patient was given treatment according to the MIS-C treatment national guidelines, developed by scientists of Vilnius University and Lithuanian University of Health Sciences, approved by Lithuanian University of Health Sciences Publishing Commission on 28 April 2022, No. 5/2022. Following national guidelines, intravenous Immunoglobulin G 2 g/kg first day and 1 g/kg the next day was given. Moreover, aspirin 30–50 mg/kg/24 hours divided into 3 times and intravenous methylprednisolone 2–3 mg/kg were prescribed for 3 days.

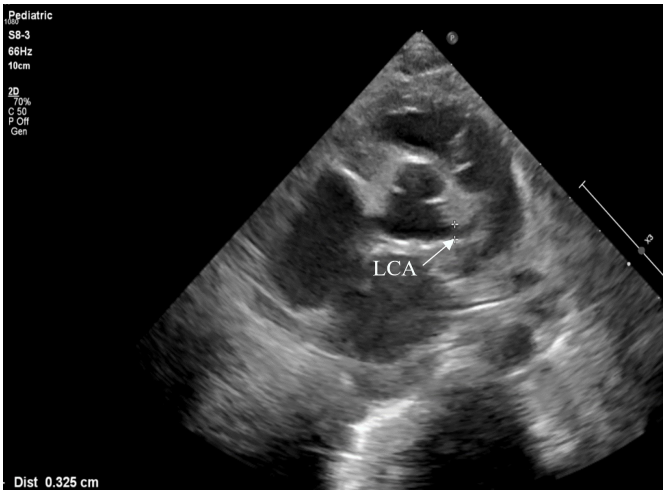

FIGURE 1. The ultrasound of the heart—view of short parasternal axis. In this view, a dilated left coronary artery is being measured (3.25 mm). LCA—left coronary artery.

Unfortunately, the state of the patient did not improve. Fatigue, general weakness and fever remained. It was decided to start treatment with interleukin-6 inhibitor Tocilizumab, administered as a single 8 mg/kg intravenous dose. This treatment had some positive results, with high-grade fever reducing, although subfebrile fever remained and the patient started experiencing intense pain of her limbs, especially during nighttime. Analgesics did not relieve pain significantly. Laboratory results showed progressed leucocytosis (67 × 10^9/L) as well as neutrophilia (61.7 × 10^9/L).

As a last resort, the biological treatment with a recombinant form of human interleukin-1 receptor antagonist Anakinra 8 mg/kg/day was started and after a week, the patient's fever disappeared, and general state of the patient increased. She no longer had fever, pain, or any other symptoms. The laboratory results showed normal levels of hemoglobin, CRP, thrombocytes, and positive changes of other laboratory results (Table 1).

After the 30 days, the patient has been discharged from the hospital. One month later, she paid a visit to a pediatric cardiologist's office and the ultrasound of the heart has been performed. There were no signs of any cardiac pathology.

5. Discussion

MIS-C is described by various multisystemic manifestations [6], therefore making it quite difficult to diagnose. The syndrome develops between 2 to 6 weeks after SARS-CoV-2. Children usually have mild symptoms of SARS-CoV-2, but as it spreads rapidly, it is crucial to test all patients for SARS-CoV-2 if the infection is suspected. For MIS-C, accurate anamnesis of the family members, as well as testing for SARS-

CoV-2 antibodies is necessary.

The patient in this case report was presented with acute abdomen as well as high grade fever.

Gastrointestinal symptoms mimicking gastrointestinal infection or inflammatory bowel disease are largely associated with MIS-C, thus doctors should consider a recent patient's exposure to SARS-CoV-2 [7].

According to systemic review regarding acute abdomen in MIS-C where a total of 385 pediatric patients with MIS-C were included, gastrointestinal manifestations were in 60.5 percent of cases, acute abdomen was in 18.7 percent of cases and laparotomy was performed in 48.6 percent of cases [8], making this clinical manifestation one not to miss.

As previously discussed, the patient was presented with high-grade fever. It is important to differentiate MIS-C and severe COVID-19. According to data, patients with MIS-C had a significantly higher prevalence of cardiac, mucocutaneous and gastrointestinal involvement and fever but a lower prevalence of respiratory involvement [9].

Kawasaki disease and toxic shock syndrome are one of the most crucial diagnoses to differentiate MIS-C with [10, 11] (Table 2). In comparison with COVID-19, Kawasaki disease and toxic shock syndrome, patients with MIS-C had thrombocytopenia, lymphopenia more frequently as well as cardiac complications, elevated markers of inflammation and cardiac damage [12]. The patient described in this case had a prolonged high-grade fever and no signs of other symptoms similar to Kawasaki disease except rash. Moreover, the blood test showed thrombocytopenia and elevated markers of inflammation.

TABLE 1. Laboratory findings of the patient with MIS-C.

Analysis (reference range)	At the beginning of the disease	After 4 weeks
Hemoglobin (110–140 g/L)	99	112
Leucocytes (5–12 × 10^9/L)	19 → 67	19
Neutrophiles (1.6–8.3 × 10^9/L)	14.7	9.9
Lymphocytes (1.2–5.8 × 10^9/L)	2	7.3
Platelets (200–582 × 10^9/L)	181	443
Alanine aminotransferase (7–45 IU/L)	161	34
Aspartate aminotransferase (8–50 IU/l)	224	34
Procalcitonin (0–0.1 µg/L)	39.4	
CRP (0–5 mg/L)	230.8	5
Troponin (0–0.04 µg/L)	0.19	
N-terminal prohormone of brain natriuretic peptide (0–26.5 ng/L)	71.1	38.1
D-dimers (0–0.5 mg/L)	10.67	3.27
Ferritin (1.2–8.8 µg/L)	>1000	854.8
Anti-SARS-CoV-2 IgG (0–28 BAU/mL)	52	

The analysis of laboratory results with presented reference rate at the beginning of the disease and after 4 weeks. SARS-CoV-2, severe acute respiratory syndrome-coronavirus; IgG, immunoglobulin G.

TABLE 2. Differential diagnosis of MIS-C disease forms.

Characteristics and symptoms of the patient	MIS-C	Kawasaki disease	Toxic shock syndrome	Patient
Patient's age	Older (6–16 years old)	Younger	Older	2 years old
Hypotension	±	−	++	−
Mucous membrane inflammation	±	+	±	−
Rash	+	+	Erythroderma	+
Desquamation of the skin of the extremities	+	+	±	−
Encephalopathy, impaired consciousness	+	Rarely	+	−
Vomiting, diarrhea, and/or abdominal pain	++	Rarely	+	++
Respiratory distress	+	Rarely	±	±
Myalgia	+	−	+	++
Coronary artery dilatation (aneurysms)	+	+	−	+
Cardiac dysfunction	+	±	Rarely	+
Heart valve regurgitation	+	+	Rarely	+
Pericardial effusion	+	±	−	+

Cardiovascular complications, especially left ventricular dysfunction, are the most common complications in patients with MIS-C [13]. Other reviews also include coronary artery dilations, aneurysms, arrhythmias, conduction abnormalities [14], as well as abnormal cardiac enzymes, mitral valve regurgitation, tricuspid valve regurgitation, aortic valve insufficiency, pericardial effusion, abnormal cardiac strain, and abnormal cardiac magnetic resonance imaging (MRI), although most of these abnormalities resolve during short-term follow-up [15]. In comparison with macrophage activation syndrome, patients with MIS-C have significantly higher chance of cardiac involvement, such as a lower left ventricle ejection fraction [16].

It has been observed that the treatment with immunomodulator had favourable early outcomes such as no mortality, left ventricle (LV) systolic function normalization, as well as a recovery of coronary arteries abnormalities [17]. In a study of New York—Presbyterian hospital, 45 children were diagnosed with MIS-C and they were followed at median time of 5,8 months; after that the results showed that even if the majority of children were critically ill, most inflammatory and cardiac manifestations resolved fast [18].

6. Conclusions

MIS-C is a difficult condition to diagnose because it can mimic other diseases. It usually presents itself with gastrointestinal symptoms such as acute abdomen and a high-grade fever. Rash is also quite common, therefore making it quite difficult to differentiate from Kawasaki disease. Laboratory results often show increased inflammation, cardiac markers, lymphopenia, and thrombocytopenia, but they are not specific. Pediatric heart ultrasound is an effective initial screening tool to evaluate a heart's function and to diagnose cardiac manifestations. It is crucial to start treatment as quick as a diagnosis is made. Immunomodulators usually have a good effect on a MIS-C. If a patient's state does not improve, immunosuppressive drugs or biology treatment might come in handy.

AVAILABILITY OF DATA AND MATERIALS

Not applicable, since it is a clinical case.

AUTHOR CONTRIBUTIONS

RŠ and SK—contributed equally to this Case Report. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

For this Case Report, Kaunas region bioethics committee does not issue the permission to publish the case reports. If the patient's case is published in such a way that neither directly nor indirectly identifies the person, then the law does not require the patient's consent (03 February 2023, No. BE-9-).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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