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Case Report

Multisystem Inflammatory Syndrome due to COVID-19 in a Newborn Patient: A Case Report from Lebanon

Oussama Skafi[1], Haidar Houmani[1], Fawzia Medlej[1], Fatima Ahmad[1], Rayan Mahfouz[1], Alaa Jazzar[2], Mohamad Cheet[1], Narjes Hazimeh[1]

[1] Department of Pediatrics, Faculty of Medical Sciences, Lebanese University, Beirut, Lebanon
[2] Faculty of Medical Sciences, Lebanese University, Beirut, Lebanon

Corresponding Author: Haidar Houmani, Beirut, Lebanon, haidar.houmani@gmail.com
This case was reported from the Department of Pediatrics at the Bahman Hospital, Faculty of Medical Sciences of the Lebanese University, Beirut, Lebanon

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Abstract

Background
Multisystem inflammatory syndrome in children (MIS-C) is a hyperinflammatory condition associated with COVID-19 in children, with features that are similar to Kawasaki disease and toxic shock syndrome. Several reports are emerging from all over the world on this condition that is associated with increased fatality rate.

Case Report
In this article, we present one of the first reports of a newborn diagnosed with MIS-C attributed to COVID-19. In addition, we discuss the diagnostic criteria and the possible pathophysiology.

Conclusion
Although COVID-19 does not frequently affect newborns, when it does, it may lead to devastating complications, such as MIS-C. As a result, providers should be on the lookout for any symptoms that can indicate a complicated infection. Further studies are still needed to develop a better understanding of the pathophysiology of this disease and establish appropriate therapeutic guidelines.

Keywords: COVID-19; Multisystem Inflammatory Syndrome; Lebanon; Case report; Newborn

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Introduction

Since December 2019, the time of emergence of the first case of coronavirus (SARS-CoV-2) in Wuhan, China, the virus has been considered as a wild variant in children. Therefore, the majority of infections in children were either mild or asymptomatic [1]. Only a small subset of pediatric patients required hospitalization. This was documented in the United States, where approximately 2% of COVID-19 cases were less than 18 years of age [2, 3].

However, in April 2020 in England, during the peak of the COVID-19 pandemic in Europe, a group of children suffering from hyperinflammatory shock with features similar to Kawasaki disease and toxic shock syndrome was reported [4]. The patients' signs and symptoms were temporally associated with COVID-19; especially since all children had serologic evidence of infection with SARS-CoV-2 [4]. Since that instance, a new spectrum of COVID-19 has emerged. On May 14, 2020, following the aforementioned reported cases, the U.S. The Centers for Disease Control and Prevention (CDC) defined this entity as "multisystem inflammatory syndrome in children (MIS-C) associated with COVID 19 [5].

In this article, we report the case of a newborn presenting with diarrhea and fever, who was found to have MIS-C attributed to COVID-19. To the best of our knowledge, this is the youngest case to be reported from Lebanon.

Case presentation

Our case is a 21 days old female newborn, delivered at term by Cesarean section due to failure to progress, with a well-followed uncomplicated pregnancy to a previously healthy mother, who presented with no symptoms and with a negative COVID-19 PCR result. She presented to our emergency department with a 4-day history of watery, non-bloody diarrhea along with 4 episodes of non-projectile vomiting. Vital signs revealed a fever of 38°C, but other vitals were within the normal limit. Further history showed no other major complaints. The mother reported a preserved per os intake and urinary output. The patient had no cough, no runny nose, nor any other upper respiratory tract infection symptoms. The parents denied any history of atopy or allergy in the family and they insisted that there was no contact between the patient and any sick or symptomatic members of the family. On physical examination, the patient was tonic and mildly hypoactive with no signs of respiratory distress. She had moderate signs of dehydration. On auscultation, clear chest sounds were heard. Upon abdominal examination, she was found to have distension and developed bilious vomiting. An urgent KUB X-ray was done, which showed dilated small bowels with no signs of obstruction or perforation, as shown in Figure 1.

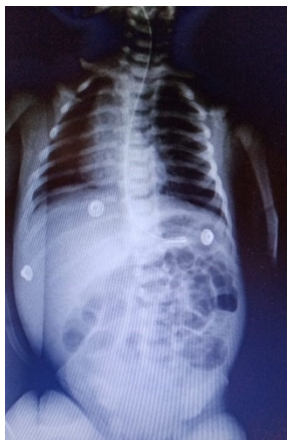

Figure 1: Abdominal X-ray showing diffuse bowel distension with no signs of perforation

The laboratory tests showed an elevated C-reactive protein (CRP) level of 99 mg/L, among other test results shown in table 1.

The patient was admitted to the neonatal intensive care unit (NICU), a full sepsis workup was performed (blood, cerebrospinal fluid (CSF), and urine cultures were taken), and broad-spectrum antibiotics (ceftazidime and amikacin) were initiated. Real-time polymerase chain reaction (RT-PCR) test for COVID-19 from a nasal swab was performed, and the result was negative. The pediatric surgery team was consulted, and they stated that a laparotomy was not needed. On the second day, the abdominal girth increased with the abdomen becoming very tense and tender as shown in Figure 2. Moreover, the girl developed jaundice, tachycardia,

and oliguria. Other laboratory tests were done and are presented in table 1 below.

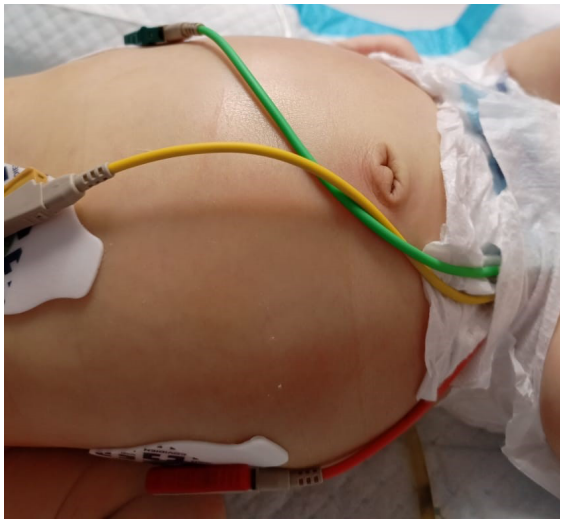

Figure 2: Abdominal distension on day 2 of admission

All the signs were indicating a scenario of shock. Thus, an appropriate hydration protocol was started with inotropes. In addition, packed red blood cells were transfused as well as pools of platelets, and fresh frozen plasma as needed. The antibiotic regimen used was escalated to meropenem, vancomycin, and metronidazole after taking a new blood culture.

The second day, an urgent laparotomy was conducted due to the worsening condition and hemodynamic instability. It revealed the presence of ileal necrosis and ischemia. An appropriate enterectomy (14 cm of the ileum) with end-to-end anastomosis was done (Figure 3). After the operation, the baby was placed on mechanical ventilation. She failed to oxygenate despite high-frequency oscillator (HFO) ventilation. Chest X-ray showed bilaterally increased alveolar-interstitial pattern compatible with bilateral pneumonia (Figure 4).

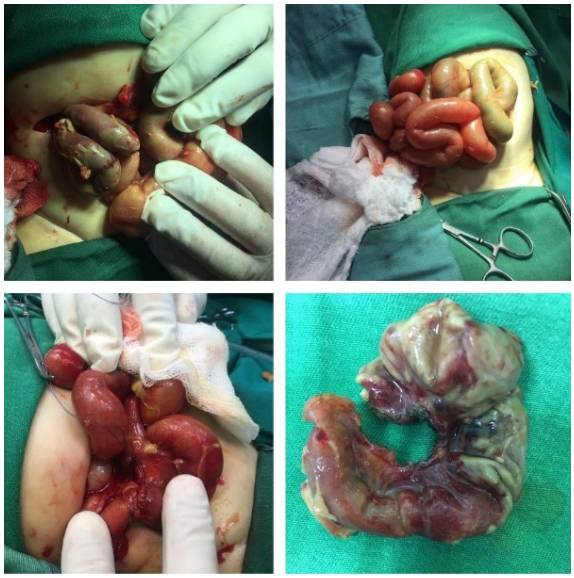

Figure 3 Terminal ileum resection and end-to-end anastomosis

After that, the girl developed generalized edema, and a maculopapular rash appeared all over the body as shown in Figure 5. She was anuric with elevated blood urea nitrogen (BUN) and creatinine levels as shown in table 1, despite the use of continuous furosemide infusion by a syringe pump. Echocardiography done showed normal heart architecture and function despite elevated troponin (0.2 ng/mL). Repeated RT-PCR for COVID-19 was negative. A high level of ferritin

Table 1: Laboratory Tests

Day of Admission	Day 1	Day 3	Day 5
Hemoglobin	13.3 g/dL	6.4 g/dL	7.25 g/dL
Platelets	549000 /mm^3	18000 /mm^3	68000 /mm^3
Lymphocytes	17000 /mm^3	15000 /mm^3	13000 /mm^3
Prothrombin time	-	72	19
Partial thromboplastin time	-	72	30
Bilirubin	-	20.4 mg/dL	8.5 mg/dL
Sodium	138mmol/L	120 mmol/L	125 mmol/L
Albumin	-	24 mg/dL	
Urea	13 mg/dL	58 mg/dL	84 g/dL
Creatinine	0.33 mg/dL	1.38 mg/dL	2.1 mg/dL
LDH	-	-	3307 U/L

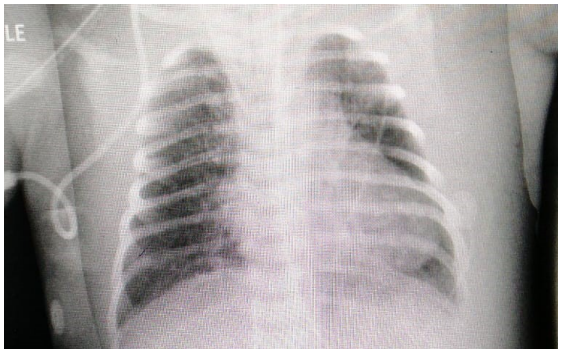

Figure 4: Chest X-ray with bilateral alveolar-interstitial pattern

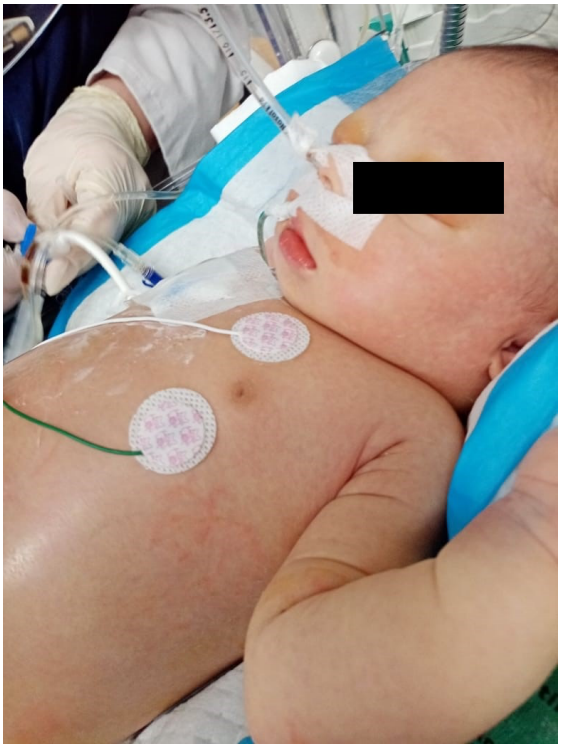

Figure 5: Maculopapular rash and generalized edema

(>40000 ng/mL), LDH (3307 U/L), and aminotransferase were found. Thus, multi-organ damage with an inflammatory syndrome was suspected.

Blood samples were taken to rule out any other infectious causes with such a spectrum of symptoms. PCR for cytomegalovirus (CMV), Ebstein-Bar virus (EBV), varicella-zoster virus (VZV), enterovirus, parvovirus, mumps, herpes simplex virus 1 and 2, parvovirus B19, adenovirus, and herpes simplex virus 6 and 7 were negative. PCR for the respiratory panel did not detect any viruses. In addition, blood, urine, and CSF cultures were sterile. Due to the current situation and high suspicion of possible COVID-19 (no other identifiable cause), the serology for COVID-19 (IgM) was taken and turned out to be positive, with an unknown source of contagion, especially that the patient's parents insisted that she didn't have any contact with strangers. We thus considered our patient as a case of MIS-C associated with COVID-19, based on the multi-organ failure presenting with kidney shutdown, hepatic failure, shock, rash, and gastrointestinal abnormalities and complications, in a context of a positive serology with no other identifiable differential diagnosis. We started intravenous steroids. Unfortunately, the baby developed cardiopulmonary arrest and passed away after 7 days of presentation.

Discussion

Since the start of the pandemic, there has been a mild presentation in the pediatric population. However, unusual presentations remain poorly understood [6, 7]. One of these presentations was the MIS-C. According to the World Health Organization (WHO), the definition of the "emerging inflammatory condition during COVID-19 pandemic" is a syndrome that can manifest in patients between 0-19 years of age [8]. Compared with their counterparts, MIS-C patients were more likely to have no underlying medical conditions (69.% vs 37.9%) [9]. To diagnose MIS-C, 3 days history of fever with 2 of the following criteria are required: *(1)* rash, bilateral nonpurulent conjunctivitis, or mucocutaneous inflammation signs (oral on the hands or feet), *(2)* hypotension or shock features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiography findings or elevated troponin/NT-proBNP), *(3)* evidence of coagulopathy (by elevated prothrombin, activated partial thromboplastin time, and D-dimers), and *(4)* acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain). In addition, the three following criteria must be fulfilled: elevated inflammatory markers, no other detected microbial cause of inflammation, and evidence of COVID-19 or contact with

patients having COVID-19 [8].

Concerning our patient, she experienced 3 days history of fever, and she presented with gastrointestinal symptoms (necrosis of the ileum), which could be due to hypoperfusion of the intestines. She also developed a maculopapular rash and coagulopathy. Cardiac injury was present with features of shock (oliguria, tachycardia, and need for vasopressors). Furthermore, our patient had elevated inflammatory markers: CRP (99 mg/l) and ferritin (>40000 ng/ml). As for other microbial causes, all the blood (repeated 3 times), CSF, and urine cultures showed no growth of staphylococcus or streptococcus. This eliminates any possible toxic shock syndrome due to these germs. In addition, a cardiac ultrasound was done to rule out Kawasaki disease, however, no coronary aneurysm was identified. Since COVID-19 has a spectrum of a Kawasaki-like illness, this favored that it is a case of MIS-C rather than Kawasaki disease. This was confirmed by positive COVID-19 serology despite the false negative RT-PCR result that can be caused by different types of clinical specimens and thermal inactivation.

In addition to the WHO criteria, the Royal College of Pediatrics and Child Health's (United Kingdom) criteria for MIS-C included the presence of lymphopenia, neutrophilia, and multiorgan damage (respiratory, nephrology, neurological, and cardiac) [10]. These findings were also seen in our patient. Several laboratory, epidemiological, and clinical features of MIS-C may differ from KD. Patients with MIS-C present with a broader age range, with shock and neurological and GI symptoms. Also, they are more likely to display cardiac dysfunction (arrhythmias and ventricular dysfunction) than children with KD [11].

At presentation, patients with MIS-C tend to have lower platelet counts, lower absolute lymphocyte counts, and higher CRP levels than patients with KD (M/H). According to the latest statistics, on March 29, 2021, the CDC mentioned 3,185 cases of MIS-C and a total death count of 36 cases. Most of the cases were children between 1 year and 14 years of age. To the best of our knowledge, no cases were reported in the newborn age period, but one of few cases was reported in an asymptomatic newborn who was positive for COVID-19 due to vertical transmission from an asymptomatic positive mother, which remains debatable [12]. However, MIS-C differs from COVID-19 illness in children and tends to be severe in infants < 1 year of age and mainly children with comorbidities, for example, asthma and obesity.

Following a SARS-CoV-2 infection, many possible mechanisms can accentuate the disease and lead to MIS-C. First, the formation of autoantibodies by antibody or cellular immunity recognition of self-antigen, such as antibodies against endothelial, gastrointestinal, and immune cells in patients with MIS-C can be implicated. Another mechanism is related to the formation of immune complexes generated by linking patient anti-spike antibodies with spike protein, which causes immune cell activation and triggers an immune-mediated injury to body tissue similar to heart and coronary injury seen in Kawasaki disease. T-cell response against SARS-CoV-2 antigens expressed on infected cells in the inflammatory process and organ damage seems to play a role in the pathogenesis [13]. Important evidence showed that the presence of angiotensin-converting enzymes, which are a major virus receptor in the GI tract, makes it an important target to the SARS-CoV-2 virus [14]. Moreover, till now, there is no current sufficient data supporting the transmission of the virus through breast milk.

Treatment is generally supportive and includes fluid resuscitation, inotropic support, and respiratory support [13]. In more serious cases, as in refractory shock and cardiac involvement with markedly elevated inflammatory markers, extracorporeal membranous oxygenation can be considered. The latter is followed by directed care against the underlying inflammatory process by intravenous

immunoglobulin, steroids, aspirin, and anticoagulation treatment. IVIG is recommended for all patients who meet the criteria for complete or incomplete Kawasaki disease, and also for patients with severe presentation and absence of Kawasaki features. Glucocorticoid treatment is suggested to be used in patients with risk of IVIG resistance, severe or refractory shock, and persistent fever with an elevation of inflammatory markers. The benefits and risks of adjunctive therapies such as interleukin-1 [IL-1] and interleukin-6 [IL-6] inhibitors, and convalescent plasma from recovered COVID-19 patients are still uncertain [15].

A pediatric rheumatologist should guide the use of these agents, and this should occur in the context of a clinical trial whenever possible. Our patient started to deteriorate and developed shock. Management was started, and the patient was diagnosed with MIS-C on the same day. IVIG was requested but due to the health situation and the economic crisis in Lebanon, it was unavailable. Thus, treatment with steroids was initiated, however, the patient passed away on the same day.

Conclusion

Although COVID-19 infrequently affects newborns, if a newborn is diagnosed with it, it can lead to devastating complications, such as MIS-C. As a result, providers should be on the lookout for it if some of these signs and symptoms are present: *Gastrointestinal symptoms such as diarrhea or vomiting, fever, rash, respiratory symptoms, abnormal blood cell count, elevated inflammatory markers, elevated cardiac markers, acute kidney injury, acute respiratory failure and shock.*

Further studies are still needed to better understand the pathophysiology of this illness and suggest appropriate therapeutic interventions.

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