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MULTISYSTEM-INFLAMMATORY SYNDROME (MIS-C) IN NEONATE ASSOCIATED WITH SARS-COVID19

Background: Multisystem-Inflammatory Syndrome in Children (MIS-C) is a rare complication of COVID-19 infection in the pediatric population which greatly enhances the risk for thrombotic complications including disseminated intravascular coagulation (DIC). Furthermore, treating complications of DIC is complex as treating one complication can exacerbate the other, and the underlying COVID-19 infection and MIS-C as a whole. This makes choosing the most appropriate treatment difficult.

Aim: To report on case of MIS-C in neonate who developed DIC with multiple thrombotic and hemorrhagic events.

Methods: In our study, we analyzed a clinical case of a neonate diagnosed with MIS-C who developed DIC with damage to the heart, kidneys, lungs, liver and adrenal glands.

Results: After infection with SARS-CoV2, MIS-C developed which led to systemic inflammation that triggered DIC, as proven by laboratory markers. DIC led to thrombotic and hemorrhagic events that affected multiple organs, which led to the following: Pre-renal Acute Kidney Injury-renal failure, acute adrenal insufficiency (Waterhouse-Friderichsen syndrome), ileofemoral thrombosis, right atrial thrombosis, Left ventricle thrombosis and fixed aortic thrombosis. Furthermore, the treatment of MIS-C and that of the complications of DIC were contraindicated on several occasions.

Conclusion: This case demonstrated that MIS-C and DIC modulated each other which worsened the prognosis for this neonate initially. With many critical comorbidities the treatment for this case became complex, treating one complication would exacerbate the other, especially noted when the neonate suffered adrenal hemorrhage. Although prognosis was poor, the neonate recovered due to precise control of treatment tactics by the multidisciplinary team.

Key words: SARS-CoV-2, MIS-C, DIC

Introduction

In late 2019, an outbreak of atypical pneumonia of an unknown etiology took place in Wuhan, China, which was later classified as corona virus disease 2019, (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and announced as a pandemic on 11th March 2020 by the World Health Organization (WHO) [1]. COVID-19 usually presents mildly in children and only in rare circumstances may cause severe disease. However, in April of 2020, the United Kingdom reported cases of 8 children that presented with hyper-inflammatory shock, and had features that were similar with the atypical Kawasaki disease (KD) or Kawasaki disease shock syndrome [2]. Although, similar to KD, it was distinct enough to deserve its own classification as Multisystem inflammatory syndrome in children (MIS-C) by the WHO. The diagnostic criteria by WHO is as follows: Age of 0 to 19 years old, Fever for 3 or more days, no bacterial or other microbial etiology, laboratory markers of inflammation, multi-organ failure with 2 or more systems being involved, and positive COVID-19 infection by PCR, serology or antigen test or exposure 3 to 4 weeks before symptoms [2]. MIS-C causes severe systemic inflammation increasing the risk for thrombotic events and can lead to Disseminated Intravascular coagulation (DIC). The rate of DIC complication in survivors is 0.6% and 71.4% for non-survivors. This depicts that when DIC complicated COVID-19, the disease course was very severe and rate of fatal cases steeply increased [3]. In this report we analyzed the progress, treatment tactics and the successful recovery of neonate with MIS-C and DIC with severe thrombotic and hemorrhagic events.

Materials. Case Report

On 03.03.2022, a 1-month-old female patient was admitted to Pediatrics infectious disease hospital with complaints of refusal of the breast, regurgitation, vomiting and diarrhea several times a day, and persistent fever lasting 3-4 days. The results of RNA virus PCR (SARS-CoV-2) were negative on admission. Treatment was viferon (interferon alpha

2b), motilium and infusion therapy. The complaints persisted and condition worsened in the evening with dyspnea.

The prenatal history was complicated. The mother had chronic arterial hypertension 1st degree, gestational diabetes, preeclampsia, anemia 1st degree at 20 weeks, SARS-CoV-2 at 30 weeks, and physiological childbirth at 40 weeks. In birth history, the birth weight and height of the patient was within normal range and she was vaccinated for BCG and HBV.

In past medical history, at 10 days of age, (05.02.22), COVID-19 infection was confirmed positive through PCR, and 5-day inpatient treatment initiated. During this period, she also developed acute bronchitis, and acute respiratory insufficiency. After inpatient treatment, she showed good recovery at that time.

On 04.03.2022, 7:50, the patient was transferred to ICU with somnolent consciousness, reduced reaction to painful stimuli, dyspnea, episodes of apnea, severe pallor of the skin and central cyanosis. Her vitals on admission were: temperature of 36 degrees Celsius (decreased due to shock and subsequent hypo-perfusion), respiratory rate of 60/min, and heart rate of 278/min which prompted an ECG and she was diagnosed with supraventricular tachycardia. Blood pressure and SpO2 were too low to be detectable and she was diagnosed with cardiogenic shock. She was then immediately intubated and put on a ventilator. At 8:00 Echocardiography of the heart revealed intraventricular septum (IVS) hypertrophy, signs of endocarditis, thrombosis in right atrium and moderately reduced myocardial contractility. At 8:49, ultrasound of hepatbiliopancreatic region revealed severe flatulence, reactive parenchymal changes in liver and bile stasis, and ultrasound signs of hypoxia of parenchyma of both kidneys. At 09:30 there was a violation of the heart rhythm, followed by cardiac arrest. After successful resuscitation, cardiac activity was restored but patient went into a coma. Ultrasound of the adrenal glands at 12:22 showed right adrenal gland hemorrhage. At 15:00, the patient had secondary ileofemoral venous thrombosis of the left lower limb confirmed by ultrasound. The left lower limb soon became necrotic (Figure 1). At 18.10, sputum examination showed Streptococcus haemolyticus 10^6, (sensitive to cefazolin, cefotaxime, ceftriaxone), indicating secondary bacterial community acquired pneumonia. Additionally, PCR testing for Cytomegalovirus (CMV), herpes simplex virus (HSV), toxoplasma and chlamydia were negative.

On 05.03.2022, she developed acute kidney injury (AKI)-renal failure, pre-renal origin, confirmed by nephrologist due to cardiogenic shock, and was put on peritoneal dialysis (Figure 2) till 08.3.2022 when kidneys function restored.

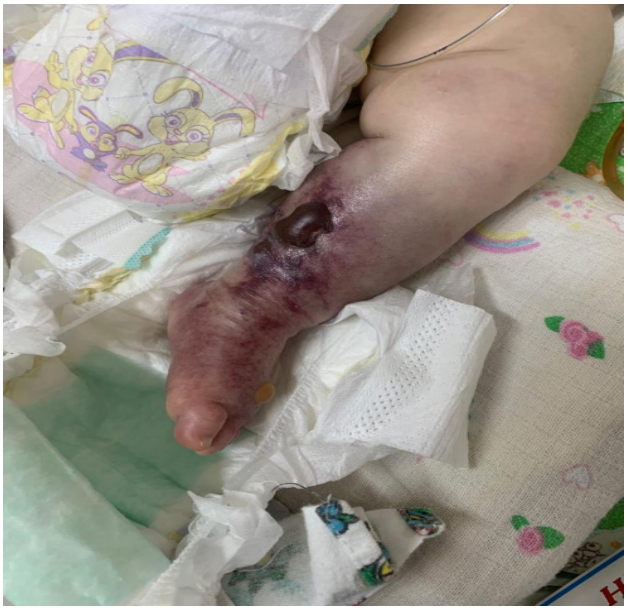

Figure 1 – Lower limb necrosis

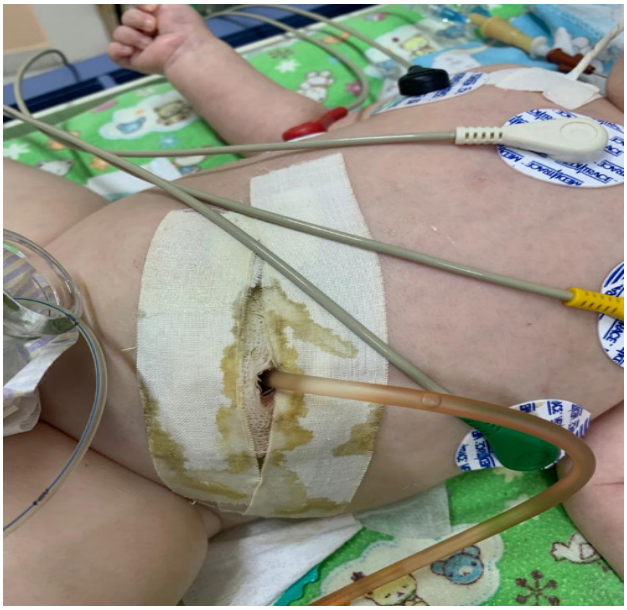

Figure 2 – Peritoneal dialysis

On the same day, 05.03.2022, MIS-C was diagnosed due to the following: persistent fever for more than 3 days, the symptom onset was around 4 weeks after positive COVID-19-PCR test, there was acute onset of clinical symptoms with right atrial thrombosis, endocarditis, right adrenal gland hemorrhage, AKI, gastrointestinal features of severe flatulence and dyspeptic symptoms, increased IL 6 and ferritin, with normal levels of CRP and procalcitonin (recorded: 04.03.2022) (table 2), marked lymphopenia neutrophilia and increased ESR in CBC (Table 1) and other microbial causes ruled out.

DIC was also confirmed on 05.03.2022, due to: thrombocytopenia and decreased hematocrit (due to adrenal hemorrhage) in CBC (Table 1), an increase in PT, aPTT and decrease in fibrinogen in coagulation profile and increased D-dimer (Table 2).

Additionally, for her CBC (Table 1), she had stage 2 anemia for most of her stay in the ICU, initially because of adrenal hemorrhage and subsequent blood loss, then later due to inflammation. Leukocytosis was present for most of her stay due to her secondary bacterial pneumonia, it normalized on 30.03 due to antibiotic treatment. As seen in Table 2, D-dimer levels remained elevated throughout her stay indicating high severity of disease and Interleukin (IL)-6 and Ferritin were high initially, then there was a rise in all indicators, and afterwards a gradual decrease in all was noted.

Table 1 – Complete Blood Count (CBC)

	04.3 (at admission to ICU)	05.3	10.3	14.3	18.3	30.3	Normal range
Hb g / l	78	96	99	101	118	109	140-240
Hct (%)	21.6	27.2	28.2	28.8	34.5	30.6	42-65
RBC (x 10^12/L)	2.11	2.77	3	3.28	3.95	3.48	3.9-5.9
WBC (x 10 ^ 9/l)	16.9	9.7	29.2	21.8	23.5	9.3	4.5-11
PLT (x 10 ^ 9/l)	173	112	33	106	121	409	150-400
ESR (mm/hour)	6	5	16	17	18	9	1-2
Lymphocytes (%)	55.4	21.5	18.4	10.9	15.6	44.3	45-75
Granulocytes (10^9/L)	9.1	6.9	21.9	18.1	18.3	3.9	1.2-6.8

Hb: Hemoglobin, Hct: Hematocrit, RBC: Red blood cell count, WBC: White blood cell count, PLT: Platelet count, MCV: Mean corpuscular volume, ESR: Erythrocyte sedimentation rate

Table 2 – Coagulation profile and inflammatory markers

	04.03 (at admission to ICU)	05.3	13.03	25.03	30.03	Normal range
Prothrombin time (s)	22.6	21.5	12.3	14.3	25.3	14-18
aPTT (s)	67.90	45.4	32.50	41.50	43.60	28-39
Fibrinogen g/L	1.10	1.9	1.00	2.15	1.18	1.5-3
D-dimer (mg/l)	8.20	0.96	23.6	10.10	9.6	Less than 0.25
Ferritin (ng/ml)	791.3	3618	2372.5	704	650	200-600
CRP (mg/l)	0.37	43.62	39.79	32.1	25	1.5-20
Procalcitonin (ng/ml)	0.176	8.37	2.38	1.95	1.5	0-0.5
Interleukin-6 (pg/ml)	30.09	-	-	-	-	Up to 29.5

CRP: C- reactive protein, aPTT: activated partial thromboplastin time

On 12.03, hepatomegaly and nephromegaly were seen on ultrasound. In table 3, a high level of ALT and total bilirubin indicates liver dysfunction, this matches with the hepatomegaly seen on ultrasound. AKI and nephromegaly resulted in increased levels of creatinine. Hypoproteinemia was significant due to severe inflammation.

Also seen in table 3, she had significant respiratory acidosis throughout her stay with significant hypercapnia. Especially on 16.03, showing decompensated respiratory acidosis. On the same day, chest x-ray showed right sided polysegmental pneumonia. On 27.03, she developed uncompensated metabolic acidosis with pronounced hyperlactatemia, low pH and low HCO3, on the same day chest x ray showed worsening right sided pneumonia with deterioration in dynamics, and she was then diagnosed with severe ventilator associated pneumonia.

Table 3 – Biochemical blood tests and Blood gas analysis

	04.3 (at admission to ICU)	06.3	10.3	16.03	26.3	28.3	Normal Range
ALT U/I	275.000	1137.000	350.000	54.000	33.000	27.000	10.000-40.0000
Total Bilirubin mmol/l	46.4	23.5	14.0	11.40	4.1	8.5	17.1-20.5
Creatinine µmol/l	65.5	66.1	162	77.2	22.6	19.2	12-62
Protein g/l	57.1	58.7	72.2	68.5	54.5	57.7	60-83
Lactate mmol/l	6.6	3.1	3.4	0.7	5.4	1.5	0.2-2.7
pH	7.3	7.28	7.19	7.08	7.19	7.47	7.25-7.45
Pco2 mmHg	43	77	68	88	41	32	35-50
HCO3- mmol/l	19.3	36.2	26.0	26.1	15.7	23.3	17-28

ALT: Alanine transaminase

Echocardiography on 24.3 showed fringed mitral and tricuspid valves with thrombus in left ventricle. Then, on 30.03, with specialist consultation, it was confirmed she has myocarditis, endocarditis due to several vegetations on anterior leaflet of mitral valve, mitral regurgitation grade 2, reduced myocardial contractility, left ventricular hypertrophy, aortic regurgitation grade 1, and fixed thrombus in ascending aorta.

Treatment

On admission to ICU, main concern was her right adrenal hemorrhage which led to acute adrenal insufficiency (Waterhouse-Friderichsen syndrome) and cardiogenic shock, she was thus given dexamethasone and dopamine. For hemostatic therapy, she was administered vikasol(vitamin K3) and etamsylate according to weight. For her supraventricular tachycardia she was given Amiodarone. The next day, for ileofemoral thrombosis, heparin was prescribed 6 times a day, dose according to weight, initiated after her right adrenal gland started stabilizing. She was also started on Cartan intravenously (IV) daily, carvedilol, captopril and spironolactone to prevent arrhythmic attack. Additionally, spironolactone and captopril served as nephro-protective agents and prevented AKI from worsening.

Treatment for MIS-C was started after slight stabilization of kidney function. Passive immunization via immunoglobulins was carried out. Bioven was administered on 06.03, 07.03 and 08.03. Then Bioven, on 31.3. Pentaglobin, was administered on 10.03, 11.03 and 12.03. Anticoagulant therapy prescribed was prescribed for her right atrial, left ventricular and fixed aortic thrombus. Fresh frozen plasma transfusiona, mainly to control her DIC, was given from 04.3 to 22.3. Furthermore, for anticoagulation, she was given hepasan from 10.03 to 21.03 against the background of Fresh frozen plasma. From 21.3 to 22.3 she was given Enoxaparin every 12 hours. Then from 03/24/2022 she was given warfarin orally. For antiviral therapy she was given Viferon (interferon alpha-2b) rectally. Antibacterial therapy for her pneumonia was started from 04.03 to 09.3 with ceftriaxone. Then, from 28.03 Vancomycin (due to worsening picture of pneumonia). Other interventions included omeprazole and almagel for gastro-protection, levimekol for treatment of necrotic surface on left lower limb, fluid infusion, intravenously, and albumin according to weight for hypoproteinemia.

Overall, there were several complications during treatment due to overlapping thrombotic and hemorrhagic complications. Especially when anticoagulant therapy was initiated, there was a high risk of hemorrhagic syndrome and so dosage and time needed to be controlled strictly.

Outcome and follow up: The patient after receiving resuscitation and intensive care therapy gradually recovered from multiple-organ failure without any long-lasting disability. The signs of lower left limb thrombosis were resolved by leaving some skin defects but not affecting limb movements. Further treatment tactics included putting the patient on daily warfarin and patient reference to the rehabilitation center and sustained follow-up by the primary care practitioners.

Discussion

We present a case of MIS in a neonate born to a mother with a history of SARS-CoV-2 infection at 30 weeks of pregnancy and showed positive PCR test result of SARS-CoV-2 at 10 days of life with moderate signs and symptoms of the infection. After being treated symptomatically at the local Pediatric Infectious Diseases hospital the patient was discharged with no symptoms of infection. The second admission of the patient was accompanied by severe symptoms including fever, gastrointestinal symptoms, atrioventricular conduction abnormalities, and evidence of coagulopathy which allowed us to suspect multisystem inflammatory syndrome. The diagnosis of MIS was based on the multisystem involvement and the presence of specific immunoglobulins for SARS-CoV-2. During the second inpatient care, the patient's condition progressively deteriorated leading ultimately to paroxysmal supraventricular tachycardia with further development of cardiogenic shock. At the time of admission to PICU (pediatric intensive care unit), the patient presented mainly with significant signs and symptoms of shock. In the beginning, it was unclear whether this condition developed from the manifested acute bacterial or viral infection which could have led to the septic shock. However, further investigation of past history laboratory tests (elevated levels of markers of inflammation, IL-6, D-dimer, PT, and PTT) and clinical examinations pointed out multisystem inflammatory syndrome. It is important to note that this patient previously had the case of SARS-CoV-2 infection with a positive nasopharyngeal swab RT-PCR test on the tenth day of life and during the second time of admission though SARS-CoV-2 infection was not detected on PCR the patient had a positive test for SARS-CoV-2 immunoglobulin (IgG) in serum. Apart from resuscitation and the measures to stabilize the patient's condition in accordance with guidelines on therapeutic management of hospitalized pediatric patients with multisystem inflammatory syndrome recommended by the CDC (Center for Disease Control and Prevention) and the NIH (National Institute of Health), intravenous immunoglobulin (IVIG) and corticosteroid, and anticoagulant therapy was initiated. However, despite elevated levels of D-dimer and thrombotic necrosis of the lower left limb, the patient developed DIC (disseminated intravascular coagulation) which forced us to discontinue unfractionated anticoagulant therapy temporarily till the condition stabilized. We assume that our report suggests both the presence of MIS-N (a multisystem inflammatory syndrome in the neonates) along with MIS-C (a multisystem inflammatory syndrome in children) which is an established entity of SARS-CoV-2[4]. The multisystem inflammatory syndrome is a relatively new condition in children, in which the exact mechanism is still unclear. It is thought to be due to immune dysregulation following exposure to SARS-CoV-2[5]. A few case reports suggest that neonatal multisystem inflammation occurs secondary to maternal SARS-CoV-2 infection [6, 7,8,9,10] which again proves our assumption on MIS-N and MIS-C. We present this case in order to increase awareness of the possibility of similar cases among pediatric care providers. We think that the maternal infection during pregnancy resulted in the development of protective IgG antibodies against the spike protein of the virus. Later these antibodies pass the placenta and through breastmilk provide passive immunity to the newborn [11]. Multiple studies suggest that the transfer ratio of IgG was more than 1.0 and there was a positive correlation between maternal and infant antibody titers [15]. However, in some genetically susceptible children, autoantibodies triggered by infection may bind to receptors in neutrophils and macrophages causing activation and secretion of pro-inflammatory cytokines that result in the development of multisystem inflammatory syndrome [13,14,15]. Additionally, we speculate that there are also antibodies produced against endothelial, gastrointestinal, and immune cells that may potentially play a role in the complexity of symptoms. As we mentioned our patient received immunomodulatory therapies (intravenous immunoglobulin and steroids), and anticoagulants (unfractionated heparin, enoxaparin, warfarin). We suggest that further studies are needed to evaluate the benefits and risks of given therapies explicitly focusing on patients with multi-organ failure (cardiac, kidney, etc.) We also admit that there were probably some medications that might be contraindicated in this kind of patient like interferons or probably overtreatment with IVIG as immunoglobulins carry a potential risk

of necrotizing enterocolitis among the neonates [16] but the complexity of the patient's condition and the potential threat of this neonate dying outweighed the other risks.

Conclusion

We conclude that history of post – SARS-CoV-2 infection in newborn and maternal history of infection for some genetically predisposed children may pose benefits as well as risks of developing multisystem inflammation with further manifestation of multi-organ failure. We recommend that in examination of neonatal patients with history of SARS-CoV-2 post-infection or born to mothers with history of SARS-CoV-2 during pregnancy MIS-C or MIS-N should be considered after carefully excluding of all potential causes of such condition in children.

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