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Neonatal MIS-C: Managing the Cytokine Storm

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Abbreviations
COVID-19 – Corona virus disease
EEG – Electroenecephalogram
HHHFNC – Heated humidified high flow nasal canula
IVIG – Intravenous immunoglobulin
LV dysfunction – Left ventricular dysfunction
MIS-C – Multisystem inflammatory syndrome in children,
MRI – Magnetic resonance imaging
RT-PCR – Reverse transcriptase polymerase chain reaction

Article Summary: A unique case of MIS-C in a newborn with refractory myocarditis along with gastrointestinal, renal and dermatological manifestations, successfully managed with IVIG and steroids.

Contributor's Statement Page
All authors conceptualized the study. Drs. Saha and Mukherjee collected data and drafted the initial manuscript. Dr. Pal coordinated and supervised data collection and critically reviewed the manuscript.
All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Abstract
A term infant girl with uneventful ante-natal history had an erythematous rash followed by fever from day 8. She was diagnosed to have late onset sepsis and treated accordingly. She received immunoglobulin for persistent thrombocytopenia, after which there was a transient improvement. The patient was transferred to our hospital on day 25, following recurrence of fever, watery diarrhea and a generalized maculopapular rash. On admission, she had tachycardia, tachypnea, anemia, thrombocytopenia, hypoalbuminemia and generalized edema. RT-PCR for COVID-19 was positive. Within 12 hours of admission, she developed cardiogenic shock with pulmonary oedema and needed invasive ventilation. Echocardiography revealed ejection fraction of 40% with mild pericardial effusion. NT-Pro BNP was 33000 gm/L, D-dimer 16500 µg/L and ferritin 16000 ng/ml. Methylprednisolone, immunoglobulin and enoxaparin was started with a diagnosis of multisystem inflammatory syndrome associated with COVID-19 (MIS-C). She developed seizures, pulmonary hemorrhage and cardiac arrest the following day along with acute kidney injury. She was extubated after 5 days. Steroid was stopped after 5 days as she developed hypertension and echocardiography had normalized. Five days after extubation, she again developed respiratory distress and was ventilated again for 2 days. Echocardiography showed moderate LV-dysfunction along with secondary elevation of ferritin. Methyl-prednisolone was restarted and continued for 5 days followed by tapering dose of oral prednisolone on which she was finally discharged. Though mild myocarditis with COVID-19 has been reported, MIS-C in a newborn with refractory myocarditis along with gastrointestinal and renal manifestations is a rare entity. Dermatological manifestation of neonatal COVID-19 is also unique.

A term infant girl with uneventful ante-natal history was noted to be febrile on day 8 with an erythematous, generalized, fleeting rash with facial sparing (pic 1a). As fever persisted, the patient was hospitalized on day 10 where she was provisionally diagnosed as late onset sepsis and started on Meropenem and Amikacin. However, noting a progressive rise in C Reactive protein with thrombocytopenia (Table 1) on day 12 she was referred to another hospital. On second admission, sepsis screen was repeated (Table 1) and blood culture grew coagulase negative *Staphylococcus aureus*. Meropenem was continued and Teicoplanin was added. Within 48 hours (day 17), she was noted to be afebrile and rashes had subsided. She received intravenous immunoglobulin (IVIG) at 1 g/kg after 2 successive days of platelet transfusions as platelet count persistently remained less than $8x10^9$/micro L. This was followed by a progressive rise in platelet count. Echocardiography was normal. Ultrasonography of abdomen showed hepatomegaly with minimal ascites. She had clinical improvement and was on oral feeds by day 17.

On day 24, fever recurred with rise in sepsis markers (Table 1). On day 25, acute onset disseminated erythematous maculopapular skin lesions were noted [Figure 1b, 1c, 1d]. There was sparing of the face with involvement of the neck, elbow, knees and a necrotic lesion in left groin. Repeat blood culture did not grow any organism. The patient was shifted to our hospital on day 25.

On admission, she was febrile, pale and tachycardic (heart rate 180-200/minute) with hepatosplenomegaly and greenish watery stool. She was hemodynamically stable and on minimal oxygen of 2 liters/min could maintain saturation of 95%. Antibiotics were changed to Cefoperazone-Sulbactum, Flucloxacillin and Clindamycin considering a differential diagnosis of staphylococcal or pseudomonal sepsis. Reverse transcriptase-polymerase chain reaction (RT-PCR) for COVID-19, which was done routinely as hospital protocol in view of the COVID pandemic, was positive on admission. Overnight there was rapid deterioration with progressively increasing respiratory distress and mixed respiratory and metabolic acidosis in arterial blood gas for which she needed invasive ventilation. Chest X-ray showed pulmonary edema and cardiomegaly. Echocardiography showed significant systolic dysfunction with ejection fraction of 40% and mild pericardial effusion. Adrenaline infusion was started and continued for 3 days. With high grade fever, and multisystemic involvement (respiratory involvement needing ventilation, cardiac involvement, dermatological involvement in the form of rash, GI involvement in the form of diarrhea) as well as high inflammatory markers like elevated CRP, ferritin, N-terminal pro B-type natriuretic peptide (NT-pro BNP) and D-Dimer, a diagnosis of multisystem inflammatory syndrome associated with COVID-19 (MIS-C) was suspected. She was initiated on IVIG 2 g/kg over 24 hours along with methylprednisolone at 2 mg/kg/day. Enoxaparin was also started at therapeutic dose (1 mg/kg/dose twice daily) which

was subsequently changed to prophylactic dose (1 mg/kg/dose once daily) as D-dimer reduced to <1500 µg/L after 7 days. We decided not to use any antiviral.

On day 27, the patient had a short duration seizure which was controlled with Phenobarbitone. Lumbar puncture was not done as she was too unstable. EEG was not done as seizures never recurred and Phenobarbitone was stopped after 5 days. An MRI scan on day 43 revealed no abnormality. On the same day (ie, day 27), she also had pulmonary hemorrhage and a cardiac arrest and was resuscitated as per neonatal guidelines. Post resuscitation she developed acute kidney injury with oliguria (Urine output 0.7 ml/kg/hr) and deranged renal function (Serum creatinine - 1.9 mg/dl). Ultrasonography of kidneys was suggestive of renal parenchymal disease with normal doppler flow in the renal vessels. She was conservatively managed with albumin (Serum albumin was 1.8 mg/dl) and furosemide. Anemia (Hemoglobin 6.7 mg/dl) was corrected with packed red blood cell transfusion. The patient was finally extubated to heated humidified high flow nasal cannula (HHHFNC) after 5 days and feeds were initiated. Bronchoalveolar lavage grew Klebsiella and antibiotics were changed to Tigecycline and Colistin in renal adjusted dose as per sensitivity reports. High resolution computed tomography (HRCT) of the thorax showed atelectasis of both lower lobes of lung. Repeat COVID-19 RT-PCR was negative at 7 days. Repeat echocardiography at day 30 suggested normal cardiac function with ejection fraction of 64%. Steroids were stopped after 5 days as the patient developed hypertension which was controlled with amlodipine and propranolol.

She developed feeding intolerance followed by a gradual deterioration of her respiratory status 5 days after extubation (day 35) and had to be re-ventilated following a failed CPAP trial. Repeat echocardiography showed moderate left ventricular (LV) systolic dysfunction, generalized LV wall hypokinesia with ejection fraction of 35- 40%. She had a second rise in

ferritin (Table 1). Milrinone was administered and methylprednisolone was restarted. The patient showed clinical improvement over the next 2 days and was extubated to HHHFNC on day 37 of life. She was febrile yet again. Bronchoalveolar lavage grew Klebsiella which was now sensitive to Meropenem which she received for 2 weeks. Feeding was re-established and sepsis markers and renal function improved over the next few days. Intra venous methyl prednisolone was given for 5 days followed by oral prednisolone. She was eventually discharged on day 50 of life on tapering dose of prednisolone, subcutaneous low molecular weight heparin (prophylactic dose) and vitamin supplements. She is well on follow-up with no further recurrence of any clinical signs of illness and normal echocardiogram with good left ventricular function and 65% ejection fraction.

Discussion

The World Health Organization described COVID-19 as a public health emergency on January 31, 2020 [1]. Severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) has affected all age groups. However, there are limited case reports in the neonatal population [2-4]. They are usually asymptomatic or present with subtle clinical manifestations [5]. There are sporadic case reports of neonates being positive for SARS-CoV-2 within 48 hours of birth. However, vertical transmission is still not an established entity [6]. In April 2020, a new syndrome related to COVID 19 was first reported in a cohort of children from the UK and subsequently from many other countries all over the world. It is given many names – multisystem inflammatory syndrome in children (MIS-C) being the most widely accepted. Although initially it was thought to affect only children, now it has also been reported in adults, though much less commonly. Both World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) has published diagnostic criteria for MIS-C (Table 2).

The first publication of a neonate with SARS-CoV-2 presented on day 17 of life with fever, cough, rhinorrhea and responded to supportive treatment [6]. COVID-19 has also been reported in a 26-week preterm neonate [7]. Neonates have reported fever, cough, rhinorrhea, apnea, tachypnoea, tachycardia, vomiting, abdominal distention and diarrhea as presenting signs. They have been noted to have elevated CRP and deranged liver enzymes. Elevated myocardial enzymes have also been noted [8].

The patient's mother was negative for COVID-19. No family members had signs and symptoms suggestive of SARS-CoV-2. She was in two different hospitals previously and may have contacted the virus there. In the first two hospitals she was not tested for COVID.

She was diagnosed on day 25 of life. She had fever, tachypnoea, tachycardia with a fleeting maculo-papular erythematous rash. There is no prior documentation of dermatological manifestation in the neonatal population affected with SARS-CoV-2. Our index case initially had an erythematous rash with central clearing on day 10 of life which may have been an early sign and was missed. She also received IVIG 1 g/kg for thrombocytopenia. Whether this dose of IVIG inadvertently made a transient improvement of signs and symptoms due to COVID which subsequently worsened will remain a conjecture. She again developed erythematous maculopapular rash with necrotic changes on her third week of life along with recurrence of fever. As the parents did not consent, biopsy could not be done.

She developed features suggestive of fulminant COVID-19 myocarditis characterized by poor cardiac contractility and elevated cardiac enzymes and NT-ProBNP and needed inotropes twice. Mild myocarditis in neonates has been demonstrated in literature [9]. She also had markedly elevated inflammatory markers and D-dimer, thereby fulfilling all the criteria for MIS-C (Table 2). Possibly this is the first reported case of MIS-C in a newborn who had

refractory myocarditis, dermatological involvement in the form of rash, gastrointestinal involvement in the form of diarrhea, renal involvement in the form of high creatinine and may be CNS involvement in the form of convulsion. She needed prolonged steroid therapy and IVIG. Dermatological manifestation as a presentation of neonatal COVID-19 has also not been previously reported.

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References

1. Zhang ZJ, Yu XJ, Fu T et al. Novel coronavirus infection in newborn babies aged <28 days in China. Eur Respir J 2020 Jun 18;55(6):2000697.
2. Fahri Ovalı. SARS-CoV-2 Infection and the Newborn. Front Pediatr. 2020 May 22;8:294.
3. Shek CC, Ng PC, Fung GPG et al. Infants born to mothers with severe acute respiratory syndrome. Pediatrics. (2003) 112:e254–6.
4. Cai JH, Wang XS, Ge YL et al. First case of 2019 novel coronavirus infection in children in Shanghai. Zhonghua Er Ke Za Zhi. 2020 Feb 4;58(0):E002.
5. Yu Y, Chen P. Coronavirus Disease 2019 (COVID-19) in Neonates and Children From China: A Review. Pediatr 2020 May 15;8:287.
6. Salvatore CM , Han JY, Acker KP et al. Neonatal management and outcomes during the COVID-19 pandemic: an observation cohort study. Lancet Child Adolesc Health. 2020 Oct;4(10):721-727
7. Piersigilli F , Carkeek K, Hocq C et al. COVID-19 in a 26-week preterm neonate. Lancet Child Adolesc Health 2020 Jun;4(6):476-478.
8. Zeng LK, Tao XW, Yuan WH et al. First case of neonate infected with novel coronavirus pneumonia in China. Zhonghua Er Ke Za Zhi. (2020) 58(0):E009.
9. Siripanthong B, Nazarian S, Muser D et al. Recognizing COVID-19-related myocarditis: The possible pathophysiology and proposed guideline for diagnosis and management. Heart Rhythm 2020 Sep;17(9):1463-1471.

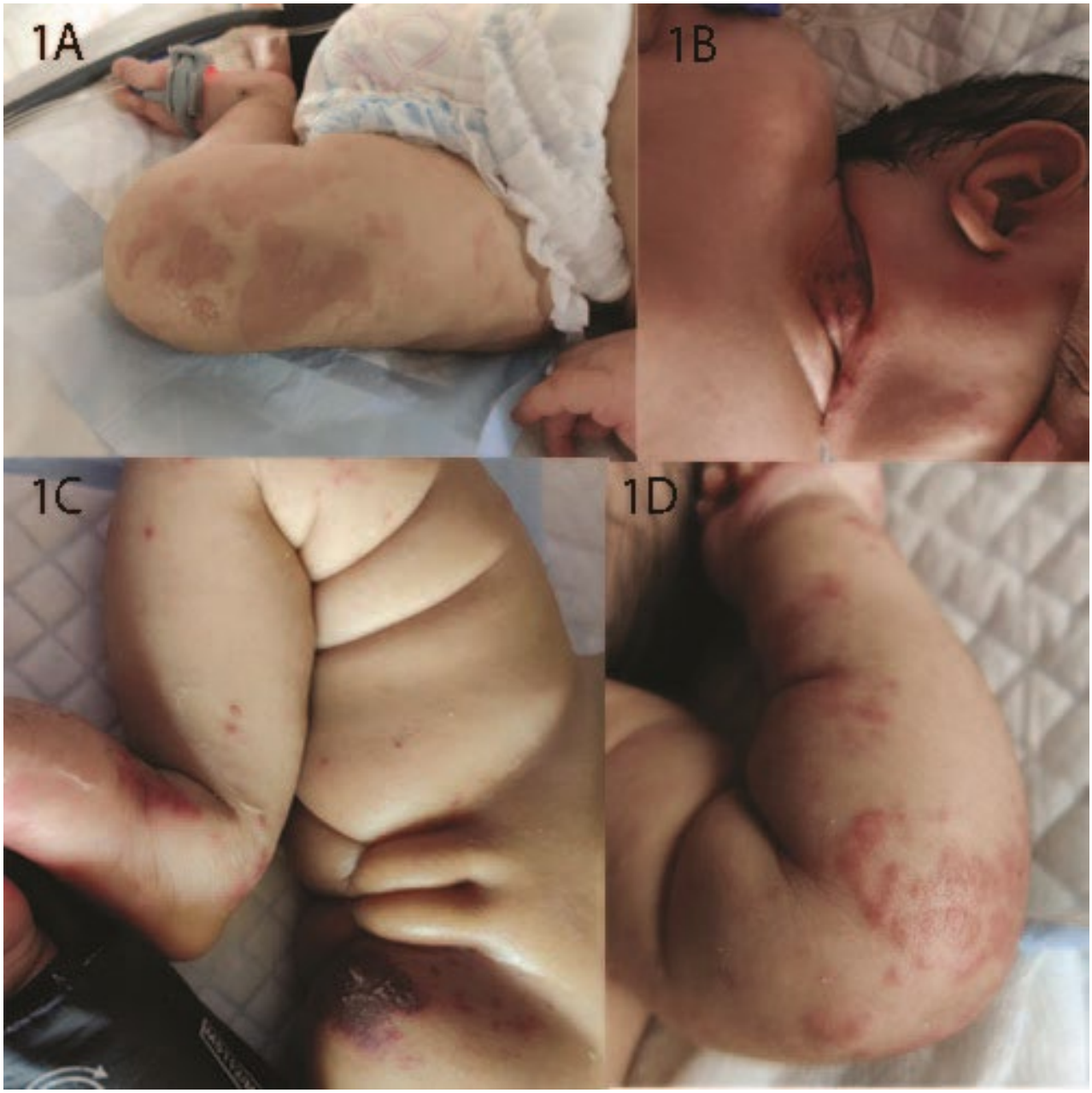
Table 1. Important laboratory parameters and echocardiogram finding

Blood	Day 12	Day 13	Day 14	Day 17	Day 24	Day 25	Day 26	Day 28	Day 33	Day 35	Day 42
Hb mg/dl	10.8	9.0	8.2	8.5	7.8	6.5	12.5	11.5	10.1	7.7	13.5
TLC/mm^3	$23x10^3$	$15x10^3$	$14x10^3$	$22x10^3$	$7x10^3$	$12x10^3$	$18.8x10^3$	$17x10^3$	$8x10^3$	$18x10^3$	$15x10^3$
DC	N78 L22	N 80 L 18	N 71 L 21	N 70 L28	N43 L55	N66 L23	N72 L20	N40 L50	N58 L36	N68 L25	N75 L18
PLT/mm^3	$105x10^3$	$10x10^3$	$5x10^3$	$110x10^3$	$90x10^3$	$100x10^3$	$130x10^3$	$150x10^3$	$80x10^3$	$135x10^3$	$135x10^3$
CRP mg/L	28	78.5	37.7	9.5	44	29	68	49	63.9	99.6	13
Ferritin µg/L		550				16,500		1702	1265	1911	
NT-ProBNP picogram/ml							33000			11,900	
D-Dimer ng/ml						16,500		1702		1265	1140
ECHO cardiography			Normal			Systolic dysfunction , EF 40%		Good LV Function EF 64%		LV Dysfunction EF- 35%	Good LV function EF 60%

Hb – Hemoglobin, TLC – Total leucocyte count, DC – Differential count, PLT – Platelet count, CRP – C reactive protein, µg – Microgram, ng - Nanogram, LV- Left ventricular, EF – Ejection Fraction

Table 2. Diagnosis of MIS-C

CDC case definition	WHO case definition
All 4 criteria must be met:	**All 6 criteria must be met:**
1. Age <21 years	1. Age 0 to 19 years
	2. Fever for ≥3 days
2. Clinical presentation consistent with MIS-C, including **all** of the following: Fever: Documented fever >38.0°C (100.4°F) or subjective fever for ≥24 hours and **2 or more** organ systems involved: • Cardiovascular (eg, shock, elevated troponin, elevated BNP, abnormal echocardiogram, arrhythmia) • Respiratory (eg, pneumonia, ARDS, pulmonary embolism) • Renal (eg, AKI, renal failure) • Neurologic (eg, seizure, stroke, aseptic meningitis) • Hematologic (eg, coagulopathy) • Gastrointestinal (eg, abdominal pain, vomiting, diarrhea, elevated liver enzymes, ileus, gastrointestinal bleeding) • Dermatologic (eg, erythroderma, mucositis, other rash) **and** Laboratory evidence of inflammation, Includes, but is not limited to • Elevated CRP, ESR, procalcitonin, fibrinogen • Elevated D-dimer, ferritin, LDH, IL6 • Neutrophilia, Lymphocytopenia. • Hypoalbuminemia **and** **Illness requiring hospitalization**	3. Clinical signs of multisystem involvement (**at least 2** of the following): • Rash, bilateral nonpurulent conjunctivitis, or mucocutaneous inflammation signs (oral, hands, or feet) • Hypotension or shock • Cardiac dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiographic findings or elevated troponin/BNP) • Evidence of coagulopathy (prolonged PT or PTT; elevated D-dimer) • Acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain)
3. No alternative plausible diagnoses	4. Elevated markers of inflammation (eg, ESR, CRP, or procalcitonin)
4. Recent or current SARS-CoV-2 infection or exposure Any of the following • Positive SARS-Cov-2 RT-PCR • Positive antigen test • Positive serology • Exposure to COVID-19 in the last 4 weeks.	5. No other obvious microbial cause of inflammation, including bacterial sepsis or toxic shock syndromes
	6. Evidence of SARS-CoV-2 infection Any of the following • Positive SARS-Cov-2 RT-PCR • Positive antigen test • Positive serology • Exposure to COVID-19 in the last 4 weeks.



Figure

1A. Erythematous rashes over legs on day 8.
1B. Erythematous maculo papular rash in neck on day 24
1C. Necrotic patch over left groin on day 24
1D. Disseminated maculopapular rash over upper arm on day 24

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