Neonatal MIS-C: Managing the Cytokine Storm

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A term infant girl with uneventful antenatal history had an erythematous rash followed by fever from day 8. She was diagnosed with late-onset sepsis and was treated accordingly. She received immunoglobulin for persistent thrombocytopenia, after which there was transient improvement. The patient was transferred to our hospital on day 25 after recurrence of fever, watery diarrhea, and a generalized maculopapular rash. On admission, she had tachycardia, tachypnoea, anemia, thrombocytopenia, hypoalbuminemia, and generalized edema. Reverse transcriptase–polymerase chain reaction results for coronavirus disease 2019 (COVID-19) was positive. Within 12 hours of admission, she developed cardiogenic shock with pulmonary edema and needed invasive ventilation. Echocardiography revealed ejection fraction of 40% with mild pericardial effusion. N-terminal pro–brain natriuretic peptide was 33000 g/L, D-dimer 16500 μg/L, and ferritin 16000 ng/mL. Methylprednisolone, immunoglobulin, and enoxaparin was started, with a diagnosis of multisystem inflammatory syndrome in children, associated with COVID-19. 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 because she developed hypertension and echocardiography had normalized. Five days after extubation, she again developed respiratory distress and was ventilated again for 2 days. Echocardiography revealed moderate left ventricular dysfunction, along with secondary elevation of ferritin. Methylprednisolone was restarted and continued for 5 days followed by tapering dose of oral prednisolone, on which she was finally discharged. Although mild myocarditis with COVID-19 has been reported, multisystem inflammatory syndrome in children in a newborn with refractory myocarditis, along with gastrointestinal and renal manifestations, is a rare entity. Dermatologic manifestation of neonatal COVID-19 is also unique.

A term infant girl with uneventful antenatal history was noted to be febrile on day 8 with an erythematous, generalized fleeting rash, with facial sparing (Fig 1A). As fever persisted, the patient was hospitalized on day 10, and she was provisionally diagnosed with late-onset sepsis and started on meropenem and amikacin. However, noting a progressive rise in C-reactive protein (CRP) 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 results revealed 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 1g/kg after 2 successive days of platelet transfusions because

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

DOI: https://doi.org/10.1542/peds.2020-042093

Accepted for publication Aug 20, 2021

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest relevant to this article to disclose.

To cite: Saha S, Pal P, Mukherjee D. Neonatal MIS-C: Managing the Cytokine Storm. *Pediatrics*. 2021;148(5):e2020042093

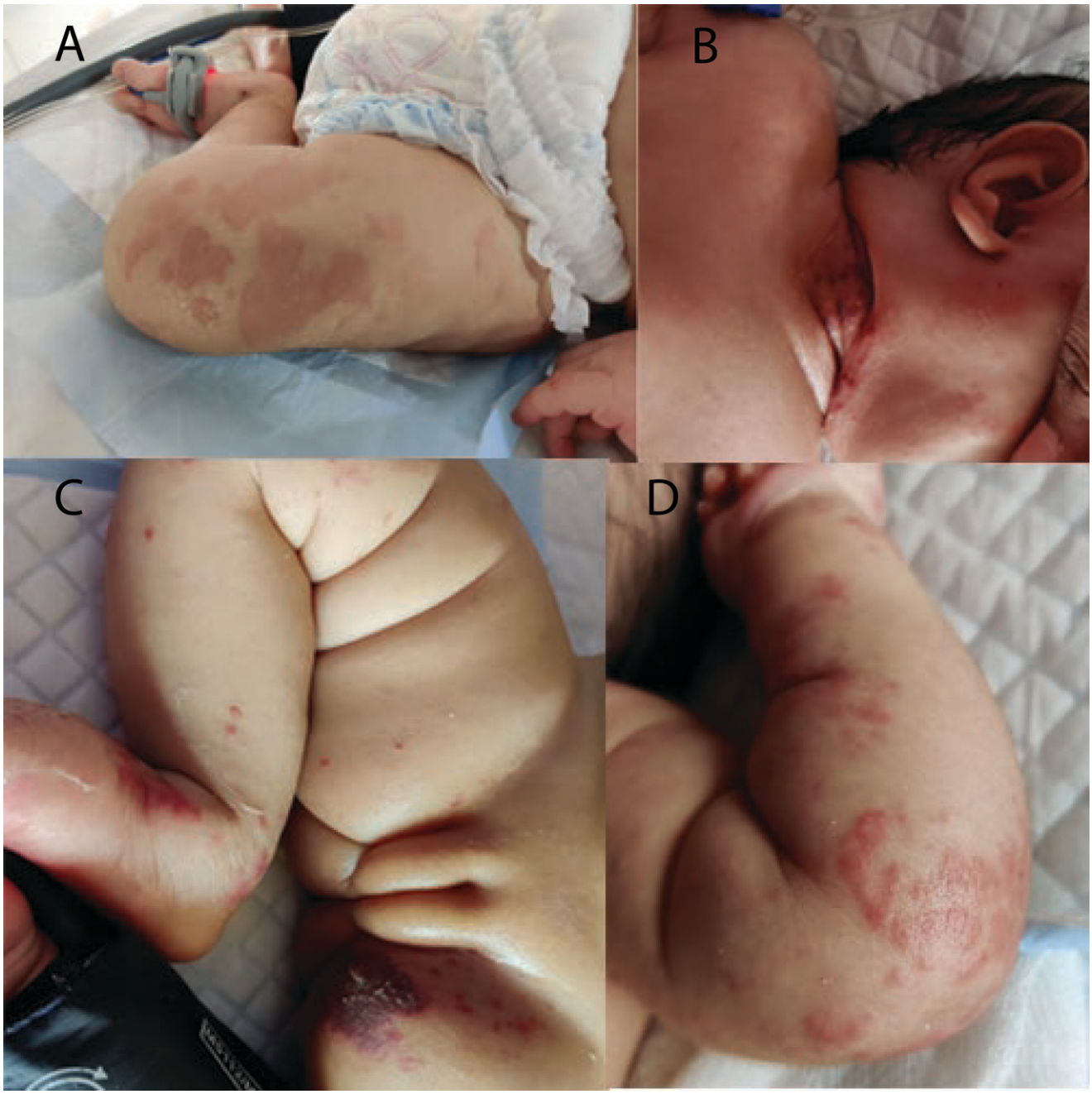

FIGURE 1

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

platelet count persistently remained $<8 \times 10^9$ per microliter. This was followed by a progressive rise in platelet count. Echocardiography was normal. Ultrasonography of abdomen revealed hepatomegaly with minimal ascites. She had clinical improvement and was on oral feeds by day 17.

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

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	23×10^3	15×10^3	14×10^3	22×10^3	7×10^3	12×10^3	18.8×10^3	17×10^3	8×10^3	18×10^3	15×10^3
DC	N78, L22	N80, L18	N71, L21	N70, L28	N43, L55	N66, L23	N72, L20	N40, L50	N58, L36	N68, L25	N75, L18
PLT, mm^3	105×10^3	10×10^3	5×10^3	110×10^3	90×10^3	100×10^3	130×10^3	150×10^3	80×10^3	135×10^3	135×10^3
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, pg/mL	—	—	—	—	—	—	33000	—	—	11 900	—
D-dimer, ng/mL	—	—	—	—	—	16 500	—	1702	—	1265	1140
Echocardiography	—	—	Normal	—	—	Systolic dysfunction, EF 40%	—	Good LV function, EF 64%	—	LV dysfunction, EF 35%	Good LV function, EF 60%

DC, differential count; EF, ejection Fraction; Hb, hemoglobin; PLT, platelet count; TLC, total leukocyte count; —, not applicable.

On admission, she was febrile, pale, and tachycardic (heart rate 180–200 beats per minute) with hepatosplenomegaly and greenish, watery stool. She was hemodynamically stable and, on minimal oxygen of 2 L/minute, could maintain saturation of 95%. Antibiotics were changed to cefoperazone-sulbactum, flucloxacillin, and clindamycin, considering a differential diagnosis of staphylococcal or pseudomonal sepsis. The result of reverse transcriptase–polymerase chain reaction (RT-PCR) for coronavirus disease 2019 (COVID-19), which was done routinely as hospital protocol in view of the COVID-19 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 radiograph revealed pulmonary edema and cardiomegaly. Echocardiography revealed 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, dermatologic involvement in the form of rash, and gastrointestinal involvement in the form of diarrhea), as well as high inflammatory markers like elevated CRP; ferritin; N-terminal pro–brain natriuretic peptide (NT-ProBNP); and D-dimer, a diagnosis of multisystem inflammatory syndrome in children (MIS-C), associated with COVID-19, 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) because 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 because she was too unstable. EEG was not done because 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 cardiac arrest and was resuscitated, as per neonatal guidelines. Postresuscitation, she developed acute kidney injury with oliguria (urine output 0.7 mL/kg/hour) 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 a packed red blood cell transfusion. The patient was finally extubated to heated, humidified high-flow nasal cannula after 5 days, and feeds were initiated. Bronchoalveolar lavage revealed *Klebsiella*, and antibiotics were changed to tigecycline and colistin in renal-adjusted dose, as per sensitivity reports. High-resolution computed tomography of the thorax revealed atelectasis of both lower lobes of lung. Repeat COVID-19 RT-PCR result 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 because the patient developed hypertension, which was controlled with amlodipine and propranolol.

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 y	1. Age 0–19 y
2. Clinical presentation consistent with MIS-C, including all of the following:	2. Fever for ≥3 d
Fever: documented fever >38.0 °C (100.4 °F) or subjective fever for ≥24 h and ≥2 organ systems involved:	—
Cardiovascular (eg, shock, elevated troponin, elevated BNP, abnormal echocardiogram, and arrhythmia)	—
Respiratory (eg, pneumonia, ARDS, and pulmonary embolism)	—
Renal (eg, AKI and renal failure)	—
Neurologic (eg, seizure, stroke, and aseptic meningitis)	—
Hematologic (eg, coagulopathy)	—
Gastrointestinal (eg, abdominal pain, vomiting, diarrhea, elevated liver enzymes, ileus, and gastrointestinal bleeding)	—
Dermatologic (eg, erythroderma, mucositis, and other rash)	—
Laboratory evidence of inflammation, including but not limited to the following:	—
Elevated CRP, ESR, procalcitonin, and fibrinogen	—
Elevated D-dimer, ferritin, LDH, and IL-6	—
Neutrophilia and lymphocytopenia	—
Hypoalbuminemia	—
Illness requiring hospitalization	—
3. No alternative plausible diagnoses	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 and/or BNP)
—	Evidence of coagulopathy (prolonged PT or PTT; elevated D-dimer)
—	Acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain)
4. Recent or current SARS-CoV-2 infection or exposure (any of the following):	4. Elevated markers of inflammation (eg, ESR, CRP, or procalcitonin)
Positive SARS-Cov-2 RT-PCR	—
Positive antigen test	—
Positive serology	—
Exposure to COVID-19 in the last 4 wk	—
—	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 wk

AKI, acute kidney injury; ARDS, adult respiratory distress syndrome; BNP, B-type natriuretic peptide; CDC, Centers for Disease Control and Prevention; ESR, erythrocyte sedimentation rate; IL-6, interleukin 6; LDH, lactate dehydrogenase; PT, prothrombin time; PTT, partial prothrombin time.

She developed feeding intolerance followed by a gradual deterioration of her respiratory status 5 days after extubation (day 35) and had to be reventilated after a failed continuous positive airway pressure trial. Repeat echocardiography revealed moderate left ventricular (LV) systolic dysfunction and generalized LV-wall hypokinesia, with ejection fraction of 35% to 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 heated, humidified high-flow nasal cannula on day 37 of life. She was febrile yet again. Bronchoalveolar lavage revealed *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. Intravenous methylprednisolone 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 LV function and 65% ejection fraction.

DISCUSSION

The World Health Organization (WHO) described COVID-19 as a public health emergency on January 31, 2020.[1] Severe acute respiratory syndrome coronavirus 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 testing 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 United Kingdon and subsequently from many other countries all over the world. It is given many names, with MIS-C being the most widely accepted. Although, initially, it was thought to affect only children, now it has also been reported in adults, although much less commonly. Both WHO and Centers for Disease Control and Prevention have published diagnostic criteria for MIS-C (Table 2).

In the first publication of a neonate with SARS-CoV-2, the infant presented on day 17 of life with fever, cough, and rhinorrhoea and responded to supportive treatment.[6] COVID-19 has also been reported in a 26-week preterm neonate.[7] Caregivers of neonates have reported fever, cough, rhinorrhoea, apnoea, 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 tested negative for COVID-19. No family members had signs and symptoms suggestive of SARS-CoV-2. She was in 2 different hospitals previously and may have contracted the virus there. In the first 2 hospitals, she was not tested for COVID-19.

She was diagnosed with COVID-19 on day 25 of life. She had fever, tachypnoea, and tachycardia with a fleeting maculopopular, erythematous rash. There is no previous documentation of dermatologic 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 1g/kg for thrombocytopenia. Whether this dose of IVIG inadvertently made a transient improvement of signs and symptoms due to COVID-19, 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 ionotropes twice. Mild myocarditis in neonates has been revealed 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, dermatologic involvement in the form of rash, gastrointestinal involvement in the form of diarrhea, renal involvement in the form of high creatinine, and maybe central nervous system involvement in the form of convulsion. She needed prolonged steroid therapy and IVIG. Dermatologic manifestation as a presentation of neonatal COVID-19 has also not been previously reported.

ACKNOWLEDGMENTS

We thank Drs Rajiv Sinha and Rajesh Singh for their contributions, help, and support.

ABBREVIATIONS

COVID-19: coronavirus disease 2019
CRP: C-reactive protein
IVIG: intravenous immunoglobulin
LV: left ventricular
MIS-C: multisystem inflammatory syndrome in children
NT-ProBNP: N-terminal pro–brain natriuretic peptide
RT-PCR: reverse transcriptase–polymerase chain reaction
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
WHO: World Health Organization

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