COVID-19-related Potential Multisystem Inflammatory Syndrome in Childhood in a Neonate Presenting as Persistent Pulmonary Hypertension of the Newborn

*Rekha Khaund Borkotoky, MD,**
*Puja Banerjee Barua, MD,**
Siba Prosad Paul, MRCPCH,†*
and Paul Anthony Heaton, FRCPCH†

Abstract: A term infant with persistent pulmonary hypertension of newborn developed clinical and laboratory features of multisystem inflammatory syndrome in childhood (MIS-C) between days 12 and 14. Mother and baby were anti-SARS-Coronavirus-2 (SARS-CoV-2) IgG positive and anti-SARS-CoV-2 IgM negative on day 18, with negative COVID-19 PCR on repeated testing; possible first documentation of neonatal MIS-C following passive transfer of maternal antibodies.

Key Words: COVID-19 pregnancy, transplacental transfer, SARS-CoV-2 IgG antibody, neonates, multisystem inflammatory syndrome in childhood

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From the *Department of Pediatrics, Apollo Hospitals (Unit: International Hospital), Guwahati, Assam, India; and †Department of Paediatrics, Yeovil District Hospital, Yeovil, United Kingdom.
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Address for correspondence: Siba Prosad Paul, MBBS, DCH, MRCPCH, Department of Paediatrics, Yeovil District Hospital, Higher Kingston, Yeovil BA21 4AT, United Kingdom. E-mail: siba@doctors.org.uk.

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Vertical transmission of SARS-Coronavirus-2 (SARS-CoV-2) to the newborn has been noted in the current SARS-CoV-2 pandemic. A meta-analysis of 176 papers documenting confirmed neonatal SARS-CoV-2 infections reported that 30% were due to vertical transmission and that 55% of infected neonates developed COVID-19 symptoms.[1] Manifestations most commonly seen included fever (44%), gastrointestinal (36%), respiratory (52%), and neurologic (18%) symptoms; radiologic imaging of the lung was abnormal in 64% of cases.[1] Case reports and series have described transplacental transfer of maternal IgG antibodies, possibly with a protective effect.[2–5] We report a potential case of multisystem inflammatory syndrome in childhood (MIS-C) from Northeastern India in a neonate initially presenting with features of persistent pulmonary hypertension of the newborn (PPHN).

CASE REPORT

A 4-hour-old male infant weighing 4.84 kg was born at 38^{+3} weeks gestation by emergency cesarean section for prolonged labor and fetal distress. Apgar scores were $7^{(1\ minute)}$ and $9^{(5\ minute)}$. Resuscitation with bag and mask ventilation was given for 20 seconds. Worsening respiratory distress, cyanosis and increasing oxygen requirement prompted transfer to a specialist neonatal unit.

The mother was 41 years (G_4P_{2+1}) and had diabetes requiring insulin during third trimester. Three weeks before delivery, she developed a febrile illness with cough lasting 3–4 days; other family members and neighbors had a similar illness. On the day of delivery, her throat and nasal swab for COVID-19 PCR were negative and remained negative on days 11 and 19 postdelivery.

On arrival to the neonatal unit, the infant was intubated immediately, and mechanical ventilation with 100% oxygen was started; during intubation, no meconium was seen below the cords. A provisional diagnosis of Persistent Pulmonary Hypertension of the Newborn (PPHN) was made although no underlying cause was evident. Chest radiograph at admission showed bilateral haze, echocardiography findings were consistent with moderate PPHN; intravenous Sildenafil, Dopamine, Furosemide and Tazobactam/Piperacillin, and intravenous fluids were started. Expressed breast milk (EBM) was given through orogastric tube. The results of laboratory investigations during the course of admission are shown in Table 1.

Improved echocardiographic findings led to extubation on day 7; but within a few hours increasing respiratory distress and oxygen requirement, and radiologic deterioration visible on chest radiograph resulted in the baby being reintubated and mechanically ventilated again, and given Meropenem. Blood cultures at admission, on days 7 and 14 showed no bacterial growth.

A computed tomography scan of thorax performed on day 12 because of deteriorating clinical condition, high ventilatory requirements and new-onset pyrexia up to 38.2ºC (lasting 48 hours) showed bilateral ground glass opacities considered consistent with COVID-19 infection although repeat COVID-19 PCR from endotracheal tube secretions remained negative. He was commenced on intravenous Dexamethasone; intravenous antibiotics, Sildenafil, and Furosemide were continued. COVID-19 serology results became available on day 18 and was positive for anti-SARS-CoV-2 IgG but not IgM.

On day 14, the baby developed features suggestive of early necrotizing enterocolitis with feed intolerance, large aspirates prefeed, increasing abdominal girth and vomiting; also, a new vasculitic rash. Feeds were stopped, and intravenous fluids and antibiotics were given for 72 hours. His condition gradually improved, and he was extubated to nasal continuous positive airway pressure support on day 16; EBM was gradually reintroduced from day 17. Inflammatory markers and D-dimer were significantly deranged (Table 1).

On day 19, both mother and baby were anti-SARS-CoV-2 IgG positive and anti-SARS-CoV-2 IgM negative. Dexamethasone was gradually tapered over 2 weeks then stopped; Sildenafil and Furosemide were stopped before discharge on day 34. At discharge, the baby was exclusively breast-feeding, neurologically stable, and had normal echocardiographic findings. He was well at follow-up after 7 days and at age 2 months; his declining antibody titers (Table 1) suggested transplacental transfer.

In view of the positive anti-SARS-CoV-2 IgG antibodies in both baby and mother, transplacental transfer of maternal antibodies was considered to have potentially contributed to the hyperinflammatory response with cytokine storm seen in the neonate. A potentially MIS-C syndrome-like presentation was thought likely with multisystem involvement including lungs, skin, gut, and heart, with raised inflammatory markers (Table 1). The initial PPHN observed may have been part of the inflammatory cascade, thus accounting for the initial presentation in the absence of significant birth asphyxia, meconium aspiration, and minimal need for resuscitation at birth.

DISCUSSION

The diagnosis of MIS-C is based on 6 criteria: pediatric age, persistence of fever, presence of laboratory markers of inflammation, manifestation of signs or symptoms of organ dysfunction, lack of an alternative diagnosis, and a temporal relation to COVID-19 infection or exposure.[6] MIS-C typically presents around 3–4 weeks after acute SARS-CoV-2 infection; many affected children have

TABLE 1. Laboratory Results During Admission

	Day 1	Day 5	Day 8	Day 10	Day 12	Day 14	Day 19	Day 21	Day 24	Day 60
White cell count (___ × 10⁹/L)	24.49	12.57		10.96	14.9	19.8	15.2		11.23	
Neutrophils (___ × 10⁹/L)	13.7	7.54		5.04	10.7	15.44	10.79		6.85	
Lymphocytes (___ × 10⁹/L)	7.8	3.65		4.93	3.12	3.57	3.34		3.71	
Platelets (150–450 × 10⁹/L)	85	70		84	216	279	242		164	
C-reactive protein (<5 mg/L)	6.5	24.4	13.2	6.7	26.8	39.1	27.9		5.3	
Albumin (2.8–4.4 g/dL)		2.5		3.1		2.2	2.7		3.0	
Interleukin-6 (0–7 pg/mL)						43.49	37.5	33.12	5.23	
Ferritin (12–327 ng/mL)						1432	902	592.3	777	
D-dimer (<500 ng/mL)						>10,000	>10,000	6542	692	
LDH (85.0–227.0 U/L)						702	668	869	309	
CK-MB (5–25 U/L)						41	34			
HS Troponin-I (<19 ng/L)						171.2	120.5	31.2	31.3	
NT-pro BNP (<62 pg/mL)						6125	5034	1750	1931	
Procalcitonin (<0.1 ng/mL)						0.532	0.421			
SARS-CoV-2 RT-PCR	Negative				Negative		Negative			
SARS-CoV-2 IgM antibodies					Negative		Negative			
SARS-CoV-2 IgG antibodies					Positive		Positive			Positive
(<1.0 Index)					59.68		14.72			6.06
Maternal							Positive			Positive
SARS-CoV-2 IgG antibodies (<1.0 Index)							24.34			14.1

CK-MB, creatine kinase myocardial band; HS, high sensitivity; IgG, immunoglobulin G; IgM, immunoglobulin M; LDH, lactate dehydrogenase; NT-pro BNP, N-terminal B-type natriuretic peptide; RT-PCR, Reverse transcriptase polymerase chain reaction; SARS-CoV-2, SARS-Coronavirus-2.

positive antibodies to SARS-CoV-2, but negative PCR at the time of evaluation for MIS-C.[6] The presentation in the infant described may be a case of MIS-C in a neonate without direct evidence of SARS-CoV-2 infection but whose mother had evidence of SARS-CoV-2 infection about 3 weeks before delivery and subsequent transplacental transfer of maternal SARS-CoV-2 IgG antibodies. The pyrexial response in neonates is usually poorly developed, and the criteria suggested for diagnosing MIS-C in children may not be entirely applicable to the neonates.

Transplacental transfer of specific SARS-CoV-2 IgG antibodies when measured in infants were similar to that of the mother and is thought to confer the neonate with passive immunity.[2–5] Analysis of EBM from 14 mothers following recovery from SARS-CoV-2 infection detected both IgM and IgG antibodies to SARS-CoV-2, confirming passive transfer of antibodies.[7]

Although harm has not been demonstrated due to the transfer of maternal IgG antibodies to SARS-CoV-2 infection,[3–5,7] from anecdotal experience in older children, antibody dependent enhancement responses have been implicated in induced immune injury where low-titer neutralizing antibodies may accentuate viral triggered immune responses causing the cascade of inflammatory cytokines.[8-10] In our case, the transfer of maternal antibodies transplacentally and through EBM may have led to a hyperinflammatory state with cytokine storm and may have been responsible for the MIS-C like presentation.

CONCLUSIONS

We believe this case to be first in the literature to report MIS-C in a neonate and highlights the importance of considering the ever-increasing spectrum of newer clinical manifestations associated with SARS-CoV-2 infection. The diagnosis of MIS-C is likely to provide the unifying explanation accounting for the clinical course of our patient. There is need for further research into neonatal MIS-C to develop criteria specific to neonates and guidance on management.

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