Case Report

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Paediatrics Section

Neonatal Multisystem Inflammatory Syndrome Associated with Passive Transfer of Antibodies

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ABSTRACT

Multisystem Inflammatory Syndrome in Children (MIS-C) is a postinfection immune-mediated condition, seen four to six weeks after Coronavirus Disease-2019 (COVID-19). Multisystem Inflammatory Syndrome in Neonates (MIS-N) is a similar hyperinflammatory syndrome seen among neonates. The exact mechanism of MIS-N is not clear. The transplacental transfer of antibodies from Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) infected mothers may lead to hyperinflammatory response among the neonates. In the current case report, the first 36-week-gestational-age male baby presented with respiratory symptoms and increased coronary Z scores which responded well to Intravenous Immunoglobulins (i.v. IG), steroids, and aspirin. The second 36-week-gestational-age male baby presented with unusual recurrent apnoeic attacks for that gestation (36 weeks) which responded dramatically to i.v IG and steroids. Immunoglobulins play a key role in the management of MIS-N.

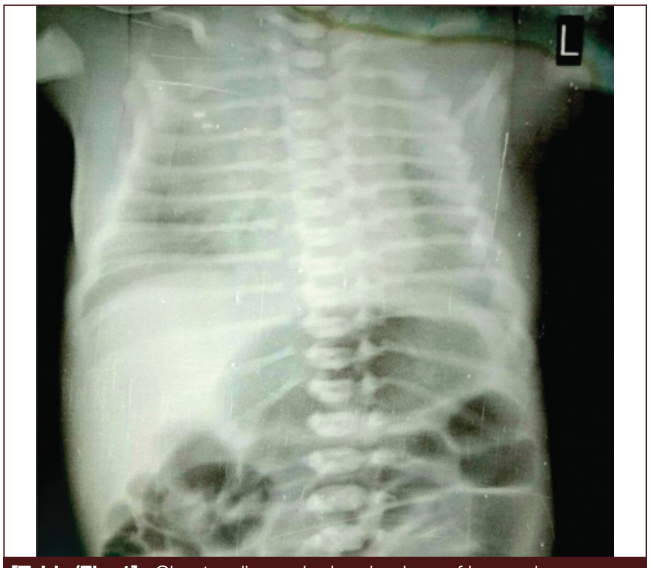
Keywords: Coronavirus disease-2019, Immunoglobulins, Neonatal hyperimmune response, Transplacental transfer

CASE 1

A 36-week-gestational-age male infant weighing 2500 grams was delivered via Lower Segment Caesarean Section (LSCS) to a primigravida mother of 24 years of age with nonconsanguineous parentage. As the baby had severe respiratory distress, the patient was referred for tertiary care.

On examination, the baby was tachypnoeic, distressed, was grunting, and had retractions, with blood oxygen saturation of 88% with two litres of nasal oxygen. Arterial Blood Gas (ABG) analysis was done and results showed pH=7.33, pCO_2=26.9, pO_2=60.6, lactate=4.7, base excess=-10.5. The baby was shifted to Neonatal Intensive Care Unit (NICU), intubated, and connected to a ventilator on Continuous Mandatory Ventilation (CMV) mode and surfactant was administered because of loss of lung volume on Chest X-Ray (CXR) [Table/Fig-1]. The baby developed a fever on day 2 of admission hence a septic screen along with blood culture was done. Reports showed C-Reactive Protein (CRP)=25.5 mg/L, Total Leucocyte Count (TLC)=12200, and Neutrophil Leucocyte (NL) ratio of 4.7, and platelets=1,32,000. Blood culture was negative.

Since, there was need for high ventilator settings, chest retractions, and fever, especially in this pandemic of COVID-19, neonatal hyperinflammatory response syndrome due to trans-placental transfer of antibodies was suspected. So, maternal and



[Table/Fig-1]: Chest radiograph showing loss of lung volume.

neonatal SARS-CoV-2 antibodies were checked, which were positive for IgG (maternal 12.5 S/Co and neonatal 13.98 S/Co, normal value <1). The inflammatory markers were CRP=25.5 mg/dL, Interleukin-6=690.87 pg/mL, procalcitonin=29.8 ng/dL, ferritin=670.82 ng/mL, Lactate Dehydrogenase (LDH)=1596 IU/L, D-dimer=10,000ng/mL, troponin=4.55 ng/mL, pro-BNP=3500 pg/mL. A 2 Dimensional-Echocardiograph (2D-ECHO) revealed

increased coronary Z-scores; Left Main Coronary Artery (LMCA)=2.9 mm (Z score=6.47), Right Coronary Artery (RCA)=2.2 mm (Z score=4.75) and pulmonary hypertension (Right Ventricular Systolic Pressure (RVSP)=46 mmHg). Based on the World Health Organisation (WHO) MIS-C criteria [1], the baby was diagnosed with MIS-N.

The baby was treated with i.v IG, 2 gm/kg; Low Molecular Weight Heparin (LMWH), 1 unit/kg; i.v dexamethasone, 0.15 mg/kg; and aspirin 3 mg/kg along with routine antibiotics and supportive care. The baby had a protracted course in the hospital with a prolonged ventilator stay (6 days), Continuous Positive Airway Pressure (CPAP) (3 days), Heated Humidified High Flow Nasal Cannula (HHHFNC) (7 days), Intensive Care Unit (ICU) (18 days), and hospital stay (21 days). During the course, the baby had recurrent seizures, feed intolerance, and high-grade fever. As the baby continued to be sick, along with the persistence of high-grade fever, 2nd dose of i.v IG was given.

With a lot of supportive management and nursing care, the baby recovered gradually and was discharged on day 23 of life. At the time of discharge, there was a significant reduction in the coronary Z-scores and pulmonary pressures LMCA=1.2 mm (Z-score-00.44), RCA=1.6 (Z score-2.52), and RVSP=23.4 mmHg. Inflammatory markers also normalised. (CRP=0.2 mg/dL, D-dimer=3280 ng/mL). The baby is on follow-up and is doing well.

CASE 2

A 36-week newborn baby boy with a birth weight of 2.7 kg was delivered by LSCS to a primigravida mother of 22 years with non consanguineous parentage. The baby was brought with breathing difficulty since birth which was gradually progressing. At the time of admission, the baby was tachypnoeic, had acral cyanosis, and blood oxygen saturation was maintained on nasal oxygen.

The initial reports were: haemoglobin=16.2 gm%, TLC=8,900, Platelet count (PLT)=4,19,000; CRP=0.3. ABG showed pH=7.23, pCO_2=49.2, pO_2=84.7, HCO_3=18.6, lactate=2.4. The baby was started on CPAP and treated with antibiotics and supportive care. On day two, the baby had a fever and recurrent attacks of apnoea and bradycardia which was unusual for that age and gestation and there was no improvement with CPAP. Magnetic Resonance Imaging (MRI) Brain was done which was normal and lumbar puncture was deferred because of the poor general condition of the baby. Blood culture was negative.f

At this point, positive maternal COVID-19 antibodies (133.3 S/Co) provided by the obstetrician guided us to check antibody levels in the baby which were positive for SARS-CoV-2 IgG antibodies (3.62 S/Co). Inflammatory markers were also elevated (D-dimers=7,620 ng/mL, LDH=688IU/L, IL6=1.13 pg/mL, Pro BNP=1325pg/mL). A 2D ECHO revealed normal coronary diameters {LMCA=1.7 mm (Z Score=2.17) RCA=1.4 mm (Z score=1.83)}. Hence, a possibility of MIS-N was considered. The patient was treated with i.v immunoglobulins 2 grams/kg, i.v dexamethasone 0.15 mg/kg, and aspirin 3 mg/kg. Baby responded dramatically and apnoeic episodes became passive within 24 hours of treatment with immunoglobulins and was weaned off to High Flow Nasal Cannula (HFNC) on day 7 and subsequently to room air on day 8. Inflammatory markers improved significantly. (CRP=0.8 mg/dL, D-dimer=1840 ng/mL). The baby was discharged on day 11 of life. The baby is on follow-up and is doing well.

DISCUSSION

The SARS-CoV-2 infection during pregnancy may lead to many prenatal and postnatal complications [2]. The current study highlighted MIS-C like manifestations among neonates. This case series explains the possibility of passive transmission of antibodies causing multi-system involvement.

In one report, the vertical transmission was presumed in a newborn by highly specific SARS-CoV-2 immunoglobulins level obtained at two hours of age, but all five Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) tests on nasopharyngeal swabs were negative [3,4]. In a study on six COVID-19 reported mothers, Zeng H et al., stated that SARS-CoV-2 was not found in the serum or throat swab by RT-PCR in any of the newborns, five babies had elevated IgG concentrations, and IgM was detected among two infants [7]. Previous reports have not indicated maternal-foetal transmission of SARS-CoV-2, including negative checks of amniotic fluid, umbilical cord blood, vaginal swabs, and breast milk [5]. The transfer of maternal antibodies transplacentally and through Expressed Breast Milk (EBM) can lead to a hyperinflammatory state with cytokine storm. These inflammatory responses among the neonates have been responsible for the MIS-C-like presentation with persistent pulmonary hypertension [6]. So in these two neonates, passive transfer of antibodies might be the cause for clinical manifestations. This was also supported by the presence of positive IgG SARS-CoV-2 antibodies in both baby and mother. In the present study, EBM is not the cause, as symptoms were seen even before the initiation of feeds.

Transplacental passage of maternal antibodies is a known fact which is also applicable to SARS-CoV-2 antibodies. Multiple studies have reported the transplacental transfer of anti-SARS-CoV-2 IgG antibodies to neonates. The majority (87%) infants born to seropositive mothers had detectable IgG antibodies at birth, transfer ratios were more than 1.0, and there was a positive correlation between maternal and infant antibody titers, regardless of the presence of symptoms in the mother or the severity of the disease [7-9]. The pathogenesis of MIS -N is not well established. It is not clear if the clinical manifestations are related to maternal COVID-19 or due to an hyperinflammatory

response produced by the transplacental passage of antibodies directed against auto-antigens [10,11].

Similar cardiac findings such as atrioventricular conduction abnormalities among older children and neonates along with response to i.v IG and steroids suggest that MIS-N may be due to passive transfer of antibodies [12]. In this series, the first baby presented with increased coronary Z scores and pulmonary hypertension which responded well to immunomodulatory therapy.

In the current case studies, both the patients received supportive management along with i.v IG and steroids, anti-platelet agents (aspirin), and anticoagulants (unfractionated heparin or LMWH) which support the earlier literature on treatment of MIS-N that the management of MIS-N includes immunomodulatory therapies, anti-platelet agents, anticoagulants and supportive treatments [13,14]. The use of iv IG should be cautiously used and more targeted therapy with these agents based on further research is prudent as i.v IG use among neonates carries the potential risk of necrotizing enterocolitis [15].

CONCLUSION(S)

Fever is very rare in neonates, and the presence of fever may be an indicator of MIS-N. Due to varied clinical presentations, a high index of suspicion is needed, especially during these pandemic times. There is a need to consider the ever-increasing spectrum of newer clinical manifestations associated with SARS-CoV-2 infection. The diagnosis of MIS-N due to passive transplacental transfer of antibodies is likely to provide the unifying explanation accounting for the clinical course of the index neonates. Further development of diagnostic criteria specific to neonates, guidance, and management of neonatal MIS-N is needed. More prospective multicentric studies are needed for a better understanding of the spectrum of manifestations of MIS-N.

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