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Case Series

Neonatal multisystem inflammatory syndrome associated with prenatal maternal SARS-CoV-2 exposure: a case series

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ABSTRACT

Multisystem inflammatory syndrome (MIS-C) in children (MIS-C) associated with severe acute respiratory syndrome coronavirus-2 (SARS-CoV2) is well recognised in children, however, rarely reported in newborns. It usually presents as fever and multiorgan involvement, with blood investigations showing increased inflammatory markers weeks after exposure to SARS-CoV-2. Unlike older children, the mechanism is unique in neonates as COVID-19 infection and the subsequent inflammatory reaction leading to MIS-C occur in two different individuals. We reviewed the perinatal history, clinical features, and outcomes of 3 neonates with features consistent with MIS-N related to maternal SARS-CoV-2, from August 2021 to December 2021. Anti-SARS-CoV-2 IgG and IgM antibodies were tested in all neonates. Clinical picture comprised multiorgan dysfunction (gastrointestinal, cardiorespiratory, haematological and dermatological), positive inflammatory markers, high ferritin and high D-dimer levels, elevated Cardiac enzymes. Blood cultures were sterile. Positive anti-SARS-CoV-2 IgG in both the mother and the infant, along with epidemiological evidence of maternal contact with COVID-19, clinched the diagnosis of MIS-C. Immunomodulatory drugs (intravenous immunoglobulin and systemic steroids) were administered. Multisystem inflammatory syndrome should be considered as a differential diagnosis in all critically ill neonates, particularly with maternal history of COVID-19 infection or epidemiological contact. This neonatal presentation is the reflection of fetal inflammatory response syndrome associated with maternal SARS-CoV-2 infection. Having no fever throughout the course of illness, in some neonates, suggests that neonates respond differently compared with children.

Keywords: SARS-CoV2, Antibodies, Intravenous immunoglobulin

INTRODUCTION

COVID-19, caused by SARS-CoV-2, is a global public health crisis with a large recent surge in India. Initial studies showed that children were spared of severe COVID-19. However, recently case reports of children experiencing a potentially life threatening pediatric inflammatory multisystem syndrome (PIMS) also known as multisystem inflammatory syndrome in children (MIS-C) have been described.[1] MIS-C is due to immune dysregulation following exposure to SARS CoV-2.[2] It typically presents as fever and multiorgan involvement, with raised inflammatory markers weeks after exposure to SARS-CoV-2.[3] MIS-C has clinical and serological similarities with Kawasaki disease. However, its pathophysiology and immunological response is dissimilar.[4,5] More than 80% of children with MIS-C have specific IgM and IgG antibodies against SARS-CoV-2, but only about 33% are positive for SARS-CoV-2 by RTPCR.[6]

Comparable manifestations have also been described in neonates. Unlike older children, the mechanism is peculiar in neonates as COVID-19 infection and the subsequent inflammatory reaction leading to MIS-C occur in two different individuals. In neonates, maternal

infection may trigger a hyperinflammatory syndrome secondary to transplacental transfer of antibodies.[7] On the other hand, the observed neonatal morbidity appears consistent with a neonatal inflammatory response syndrome to maternal viral infection.[8]

Vertical transmission of SARS-CoV-2 infection to the fetus is uncertain.[9] Studies found that, the placenta has low expression of canonical receptors essential for viral entry, which may explain the rarity of vertical transmission of the virus.[10] A systematic review and meta-analysis found inconclusive evidence for in-utero transmission among 1316 pregnant women across 39 studies.[11]

We present a case series of 3 neonates with multisystem involvement, hyperinflammatory syndrome and positive anti-SARS-CoV-2 IgG antibodies, temporally related to maternal antenatal SARs-CoV-2 exposure, where all the mothers were asymptomatic and COVID RTPCR negative at the time of parturition, in a tertiary care hospital.

CASE SERIES

Case 1

A singleton female neonate 36 weeks of gestational age with a birth weight of 1600 gm was delivered by elective caesarean section to a 30-year-old female primigravida. The mother did not have any significant medical history. Antenatal ultrasonography scan at 36 weeks of gestation reported as mild fetal ascites and pleural effusion; absent diastolic flow and altered CP ratio causing brain sparing effect, IUGR, fetal bradycardia suggesting non-immune hydrops fetalis. The neonate did not require resuscitation, and Apgar scores were 7 and 8 at 1 and 5 min, respectively. Neonate was admitted to NICU immediately after birth in view of mild respiratory distress. Apart from respiratory distress, neonate had tachycardia, cold peripheries, prolonged capillary refill time of >3 sec and grade 2 murmur on admission. Non-invasive (CPAP) respiratory support was provided along with fluid bolus and ionotropic support. Blood culture was drawn and intravenous antibiotics were initiated.

Laboratory investigations showed white blood cell count was 11700 cells/µl and platelet count 47000/µl. Abdominal ultrasonography was reported as mild ascites with hepatic congestion. USG brain was normal. CRP was reported positive. Suspecting early-onset sepsis, antibiotics were stepped up to vancomycin and cefoperazone sulbactam. In spite of all interventions tachycardia and murmur were persistent, hence 2D ECHO was done, which was suggestive of coronary aneurysms; RCA=1.9 mm (+4.3); LMCA=1.8 mm (+3.2), trace pericardial collection with 45-50% LVEF.

Considering the current pandemic scenario, inadequate response to treatment and ECHO report, anti-SARS-CoV-2 antibody serology test was performed. The Neonate was reactive for anti-SARS-CoV-2 IgM as well as IgG. The mother was reactive for anti-SARS-CoV-2 IgG. Inflammatory markers were raised. Serum ferritin (245 ng/ml, normal range: 15-200 ng/ml). Cardiac enzyme N-terminal-pro-B-type natriuretic peptide was elevated (17423 pg/mL, normal range:<125 pg/mL), cardiac troponin T (0.5 ng/ml, normal range: 0.01-0.06 ng/ml), so was lactate dehydrogenase (LDH) (396 units/L, normal range: 10-25 units/L). D-dimer levels (2.1 mg/l, normal range: 0-0.5 mg/l). Blood culture was sterile. Clinical picture comprising multiorgan dysfunction, positive inflammatory markers, high ferritin, D-dimer levels, along with positive serologies in both mother and infant fitted into a hyperinflammatory process probably MIS-N. Intravenous immunoglobulin (IVIg) was administered (2 g/kg). Injectable furosemide along with intravenous methylprednisolone (2 mg/kg/dose) was initiated.

On day 7, baby developed altered RT aspirate. Repeat investigations revealed severe thrombocytopenia (platelet count <20000/ µl) and deranged coagulation profile. FFP and RDP transfusion were given. Ophthalmological examination for fundus was normal. Improvement in respiratory distress and tachycardia were observed on day 3 of treatment. Baby was started on RT feed, tolerated well. Repeat 2D ECHO after 5 day reported normal LV function and decreasing size of RCA (1.3 mm) and LMCA (1.5 mm). With improvement of respiratory distress and tachycardia, respiratory and ionotropic support were tapered gradually and stopped. Repeat laboratory parameters showed an improving trend with declining ferritin, LDH, D-dimer, troponin T levels. Injectable methyl prednisolone was discontinued after 5 days and oral prednisolone was started. Baby was discharged on day 15 of life after established breast feeding, on oral steroids (tapering course), oral ranitidine and oral supplements with stable status. Repeat echocardiography after 2 weeks was normal without any dilatation of the coronaries.

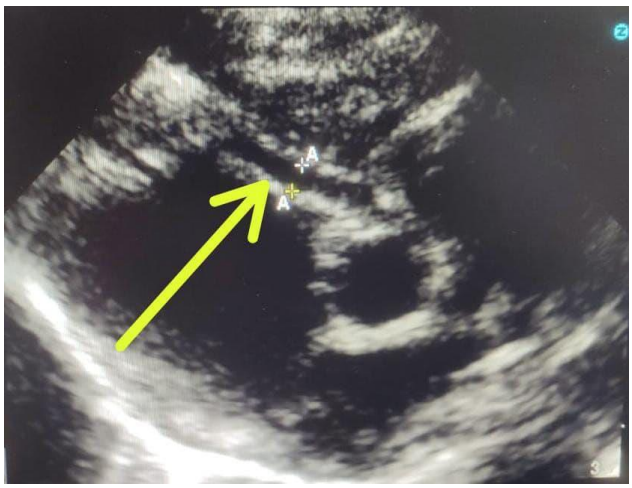

Figure 1: Small aneurysm of coronary (Z-score 4.3) (case 1).

Case 2

A 34-week (gestational age) female new-born, weighing 2700 gm, was delivered by an emergency caesarean section, due to placental previa and history of PV leak. 25 years old Mother was case of gestational diabetes mellites. Baby cried immediately after birth with Apgar score 7 and 9 at 1 and 5 min respectively. Baby was admitted in NICU as it was premature baby born to gestational diabetic mother. On admission baby was euthermic, the chest was clear, grade 2 murmur, CRT <3 sec, did not have any respiratory symptoms and was having normal oxygen saturation on room air. Neither neurological or musculoskeletal abnormalities nor dysmorphisms were noted. Feed was started but the oral intake was poor. Baby was maintaining blood sugar levels. Laboratory investigations showed leucocytosis with lymphopenia (WBC count-11000 cells/µl), thrombocytopenia (platelet count 47000/µl) and positive CRP.

IV antibiotics were started in consideration to PV leak and positive CRP report. Chest x-ray was normal lung field without cardiomegaly. The electrocardiogram showed sinus rhythm and the point-of-care echocardiogram at 48 hours showed PDA (2 mm), dilated coronaries RCA=1.6 mm (+2.5); LMCA=1.4 mm (+1.4) with normal LVEF.

Considering the current pandemic situation and ECHO report, anti-SARS-CoV-2 antibody serology test was performed. On day 3 both mother and baby were reactive for anti-SARS-CoV-2 IgM as well as IgG. Mother was asymptomatic and throat swab tested negative for SARS-CoV-2 PCR. Inflammatory markers were requested. CRP was positive serum ferritin (125 ng/ml), serum lactate dehydrogenase (LDH) (2372 units/L), cardiac troponin T (0.09 ng/ml), D-dimer levels (1.16 mg/l). Blood culture was sterile. Intravenous immunoglobulin (IVIg) was administered (2 g/kg). subcutaneous low molecular weight heparin (1 mg/kg) along with intravenous methylprednisolone (2 mg/kg/dose) was initiated. On day 6, platelet count were improved, CRP was negative decreasing serum ferritin (65 ng/ml and serum LDH levels (732 units/L). Intravenous methylprednisolone was discontinued after 3 days when the oral prednisolone was started.

Repeat 2D ECHO on day 10 suggest improving coronaries dilatation without any thrombus or collection. There were normalisation of troponin T levels (0.01 ng/ml). The D dimer level was persistently raised (1.22 mg/l). Low molecular weight heparin was stopped and baby was started on oral aspirin (3 mg/kg/day). Baby was discharged on day 13 of life after established breast feeding, on oral steroids (tapering course), aspirin and oral supplements with stable status. Follow up echocardiography, 2 weeks after discharge was normal. D dimer was normal.

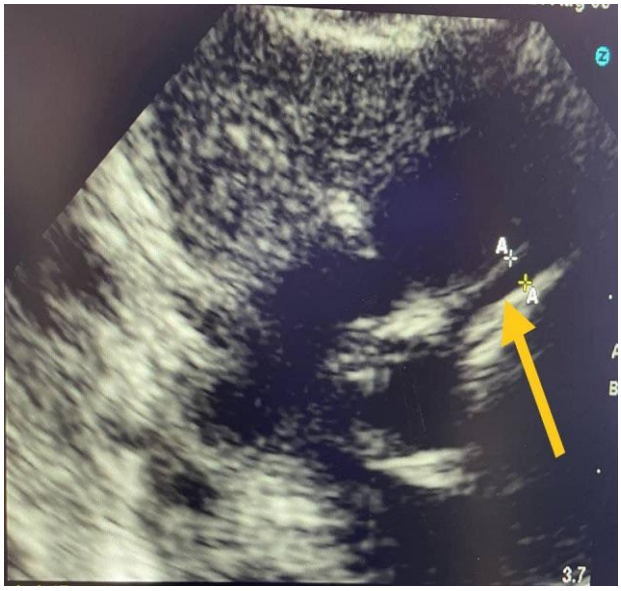

Figure 2: Dilated coronary (Z-score 2.5) (case 2).

Case 3

A 4-day-old term female new born (weight 2500 gm) with normal antenatal and perinatal history presented with poor feeding and reduced activity. The baby was exclusively breastfed. The mother had history of fever, cough, cold in third trimester. The baby was seen in the post-natal ward by a paediatric doctor. On examination, the baby was lethargic, reduced tone, sluggish reflexes including Moro, absent suck, no bulging of the anterior fontanelle, grade 4 pansystolic murmur, no respiratory distress, clear chest. Blood sugar level was low. An intravenous bolus of 10% dextrose (2 ml/kg) was given. The baby was admitted with suspected late-onset sepsis. Initial glucose infusion rates maintained at 6 mg/kg/min, blood culture was drawn and intravenous antibiotics were initiated. Initial investigations showed negative septic screen, normal cerebrospinal fluid analysis. On day 2 of illness, baby developed seizure with arching and up rolling of eye balls. Blood sugar level was normal. Levetiracetam was given as a loading dose at 30 mg/kg. Other supportive treatment was given.

On day 3 of illness, baby had tachycardia, tachypnea, respiratory distress, poor peripheral perfusion. X ray chest suggestive of cardiomegaly. Oxygen support was given. Intravenous furosemide (1 mg/kg) and infusion dobutamine (10 µg/kg/min) were initiated. Antibiotics (piperacillin-tazobactam and amikacin) were stepped up. 2D ECHO reported as large peri membranous VSD, ASD (4 mm), dilated RA and RV. USG brain and abdomen was normal. Blood culture was sterile. On day 4 of illness, both mother and baby were reactive for anti-SARS-CoV-2 IgG. CRP was positive. Raised serum ferritin (340 ng/ml), raised serum lactate dehydrogenase (LDH) (1118 units/L), D-dimer levels (7.94 mg/l). In the absence of other plausible explanations, led us to consider the possibility of a hyperinflammatory response

to prenatal exposure to COVID-19 intravenous immunoglobulin (IVIg) was administered (2 g/kg). Intravenous methylprednisolone (2 mg/kg/dose) was initiated.

On day 6 of illness, baby developed maculopapular rash with erythematous base over chest and abdomen. These rash was conservatively managed with topical antibiotic (mupirocin ointment twice daily). Rash resolves over a period of 2 days with crusting. Decrease in serum ferritin (202 ng/ml), and serum lactate dehydrogenase (LDH) (943 units/L).

Subsequently neonate developed bleeding tendency associated with thrombocytopenia and deranged coagulation profile. Neonate received RDP and FFP transfusion. The infant was electively intubated in view of increase respiratory distress and worsening shock and was continued on mechanical ventilation. Inotropic support (injection dopamine at 10 mcg/kg/min followed by injection nor adrenaline at 0.2 mcg/kg/min) was initiated, following which blood pressures were within the expected range. In view of multiorgan involvement and shock, repeat dose of IVIg was considered. Eventually, neonate had bleeding in endotracheal tube and succumb to illness due to profuse pulmonary haemorrhage.

DISCUSSION

In this report we have accounted for three cases of Neonatal multisystem inflammatory syndrome, contributing to premature labour, respiratory distress, and multisystem organ involvement. This adds to the growing evidence pointing to the potentially devastating neonatal outcomes. Neonates impacted by MIS-N would present with varying degrees of multi-organ system involvement (GI, cardiac, respiratory, haematological, hepatic and dermatological) and high morbidity.[12]

Molecular mechanisms underlying MIS-C are not fully understood. Consiglio et al showed that the pathophysiology of MIS-C is distinct from the cytokine storm of severe acute COVID-19 as well as from the inflammatory response of Kawasaki disease, in addition to finding evidence of autoantibody-mediated pathology.[14] Diagnosing MIS-N in neonates is even more challenging. MIS-N is proposed to be a disease manifestation of antibody-mediated immune activation affecting various organs rather than the infection itself.[15] Moreover, the clinical manifestations of MIS-N are very similar to sepsis like illnesses and other conditions associated with prematurity, making it difficult to differentiate between them on clinical grounds alone.[16] Fever may be a less reliable diagnostic criterion in neonates, particularly those born preterm.[17] Our patient (case 1 and 2) had cardiac involvement including significant dilatation of coronaries, (case 3) had neurological symptoms including seizures and dermatological involvement. All cases had respiratory and haematological involvement.

MIS-N is characterized by elevated CRP and serum ferritin which correlate sometimes with leukocytosis and lymphocytopenia; it is often associated with thrombocytopenia.[18] Leukocytosis and thrombocytopenia were demonstrated in all three cases. Elevated levels of CRP, serum ferritin, serum LDH were demonstrated in all cases with the evidence of inflammation and multisystem involvement.

Our patient's echocardiogram (case 1) showed a small aneurysm (Z-score 4.3), with compromised ventricular function (Figure 1), whereas case 2 had dilated coronaries (Z score 2.5), but ventricular function was preserved (Figure 2). Z-score of 2 to <2.5 is considered to be dilated and >2.5 to <5 is considered to be small aneurysm. Z-scores for coronary artery measurement and interpretation using nomograms in smaller babies again pose a big challenge.[19] Typical skin manifestation in our patient have been described by Kappanayil et al.[20] Similar to previous reports, skin lesion in our index case healed with conservative measures. Presence of such skin lesions in a symptomatic neonate can point towards MIS-C.

The management of patients with MIS-N requires shock control, immunomodulatory therapy, and the usage of thrombo-prophylaxis agents.[21] Immunomodulatory therapy particularly intravenous immunoglobulin, corticosteroids, and interleukin-1-receptor antagonist (anakinra) have been successfully used for treatment.[18] IVIG should be judicially used, even ventilated baby can be managed with proper venti-care and chest physiotherapy.[22] Clinical conscious weighs greater than just treating laboratory reports. As MIS is inflammatory process, with limiting role of antibiotics; antibiotics should be judicially used.[23]

Deranged D dimer levels were present in all three cases. Prolong aspirin therapy is given in the babies, who required low molecular weight heparin (LMWH). Decreasing and normalizing levels of D-dimer were documented before discontinuation of LMWH.

This report suggests the presence of multisystem inflammatory syndrome in neonates (MIS-N) along with MIS-C, which is an established entity of COVID-19 disease among children. This neonatal presentation is the reflection of fetal inflammatory response syndrome associated with maternal SARS-CoV-2 infection.[24] Having no fever throughout the course of illness, in some neonates, suggests that neonates respond differently compared with children.[14] It might be important to re-evaluate the current criteria of MIS-C to be generalizable to neonates or to develop new criteria for diagnosis of multisystem inflammatory syndrome in neonates.[25]

These cases highlight the need to better understand the effect of COVID-19 on the maternal-fetal dyad. It might

have important implications for healthcare professionals looking after neonates, and also for the postnatal counselling and care of infants born with antenatal exposure to COVID-19. With pregnant women, globally, becoming more vulnerable to COVID-19 exposure because of relaxation of restrictions and setting in of pandemic fatigue, protecting the maternal-fetal dyad from SARS CoV-2 through appropriate vaccination strategies and other measures might become an important public health need.

CONCLUSION

Multisystem inflammatory syndrome should be considered as a differential diagnosis in all critically ill neonates, particularly with maternal history of COVID-19 infection or epidemiological contact. Considering clinical manifestations in newborns and supportive investigations, if we consider appropriate and on-time interventions to inhibit cytokine cascade inflammations, mortality and morbidity caused by inflammation and relative complications can diminish.

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