Case Report

Multisystem inflammatory syndrome in neonates due to severe acute respiratory syndrome coronavirus 2: An emerging entity

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 was declared as a pandemic in March 2020. The virus has affected more adults than children, with disease severity being lesser in children. We present a case of a neonate who tested positive for coronavirus disease 2019 infection on day of life 3, 6, and 15. The baby had fever, respiratory distress, and shock. Laboratory investigations showed raised inflammatory markers, raised D dimer suggesting coagulopathy, coronary dilatation on 2D echocardiogram, and raised N terminal pro-brain natriuretic peptide. The neonate was successfully treated with good supportive care, lung-protective ventilatory strategies, early intravenous immunoglobulin administration, corticosteroids, and remdesivir.

Key words: Coronavirus disease 2019, Fetal inflammatory response syndrome, Multisystem inflammatory syndrome in children, Multisystem inflammatory syndrome in neonates, Neonate, Severe acute respiratory syndrome coronavirus 2

Multisystem inflammatory syndrome in children (MIS-C) after coronavirus disease 2019 (COVID-19) infection is an entity that was first described in Europe and North America when clusters of children were found to have features similar to Kawasaki disease and toxic shock syndrome in the presence of COVID-19 infection. Severe acute respiratory syndrome coronavirus 2 (SARS CoV2) elicits a hyper-inflammatory reaction in the host, leading to multiorgan involvement and hence develops features of MIS-C. The incidence of MIS-C in <21 years is 5.1/1,000,000 persons per month [1]. The mortality rate of MIS-C was found to be 2.2% in a systemic review of 17 case series [2]. The number of cases seen in neonates is comparatively very few. Furthermore, the mechanisms involved in the pathogenesis of this condition in neonates are different. Here, we present one such case report of neonatal MIS after COVID-19 infection of both mother and baby.

CASE REPORT

An out born neonate was referred to our hospital on 17 days of life (DOL). The neonate was delivered at term through vaginal route to a gravida-3 mother, cried at birth with history of meconium-stained liquor. The baby had respiratory difficulty at birth with Downe's score-4 requiring non-invasive ventilation on DOL 1. Chest X-ray revealed no significant abnormality. As clinical examination showed signs of impending shock with respiratory distress on DOL 1, the baby was started on inotropes. Sepsis screen was negative. Injections cefotaxime and amikacin were started. Mother had a history of fever 3 days before delivery and the reverse transcription polymerase chain reaction (RTPCR) for COVID on post-partum day 2 was positive. On DOL 3, the baby started having fever spikes for which a repeat sepsis screen was done which was negative. The COVID RTPCR of the baby's oropharyngeal swab sent turned out to be positive. Inotropes were discontinued on DOL 3 as shock resolved. On DOL 4, the baby had focal convulsions for which evaluation was done; serum electrolytes, ionic calcium levels, and blood sugar levels were within normal limits and cerebrospinal fluid analysis showed no abnormality. Persistent fever spikes and repeat COVID RTPCR swab were positive on DOL 6. Moreover, the background of the mother being COVID positive and aforementioned clinical picture raised suspicion of inflammatory response syndrome (IRS). Detailed workup for the same was done. 2D echocardiogram (ECHO) showed coronary artery dilatation (proximal left coronary artery measuring 3 mm in diameter). Inflammatory markers were raised (Table 1). The baby fulfilled the criteria of MIS-C as per the World Health Organization (WHO) case definition and was started on intravenous immunoglobulin (IVIG) at a total dose

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Table 1: Investigations

Investigations	DOL 2	DOL 6	DOL 20
Hb/WBC/Platelet	15.2/18,300/290,000	15.6/9400/279,000	16/11,500/434,000
DLC(P/L)	85/12	70/25	75/20
CRP (mg/L)	3.2		3
D dimer (ng/ml)		5679	402
Ferritin (ng/ml)		877	223
IL 6 (pg/ml)		110	38
Na/K (mEq/L)		141/4.2	
RBS (mg%)		98	
NT pro-BNP (pg/ml)		>35,000	
PT (sec)/INR/aPTT (sec)		14/1.0/26	

Hb: Hemoglobin, WBC: White blood cells, DLC: Differential leukocyte count, CRP: C-reactive protein, IL 6: Interleukin 6, Na/K: Sodium/potassium, RBS: Random blood sugar, NT pro BNP: N terminal pro-brain natriuretic peptide, PT: Prothrombin time, aPTT: activated partial thromboplastin time, DOL: Days of life

of 2 g/kg over 2 days. The baby continued to have fever spikes, raised inflammatory markers with an increased requirement of ventilatory support, and worsening oxygenation index 28 suggestive of severe acute respiratory distress syndrome. Hence, injection methylprednisolone was given at 10 mg/kg/day for 7 days, and injection remdesivir was given for 5 days (5 mg/kg on the first day, followed by 2.5 mg/kg on the next 4 days). Clinical improvement was seen along with improvement in laboratory parameters. The patient was brought to our hospital on DOL 17 because of financial constraints. The patient was weaned off ventilator and successfully extubated on DOL 19 and weaned off oxygen support by DOL 22. COVID-19 RT PCR done on admission to our institute was negative. Inflammatory markers showed a declining trend. 2D ECHO was repeated on DOL 20 which was normal. High resolution computed tomography of the thorax (Fig. 1) was done which was suggestive of changes typical of COVID pneumonia (CORADS 5, moderate severity, score-14/25) and fibrotic changes in the lung (Fig. 1). The baby recovered and was successfully discharged on DOL 26.

On follow-up after 6 months, the child was asymptomatic, off antiepileptics and had no further complications.

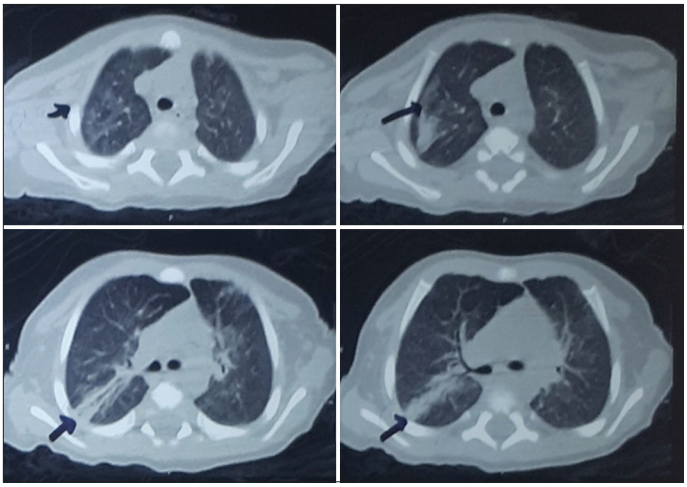

Figure 1: Original photo of high resolution computed tomography thorax of the patient showing fibro atelectatic changes in lung parenchyma

DISCUSSION

SARS CoV2, though less commonly, affects children with a propensity for more severe infection in infants [3], the incidence of COVID-19 infection in neonates born to COVID-19 positive mothers is 11.64% [4]. In utero infection of the fetus with COVID-19 from infected mother (vertical transmission) is highly suspected, but there is not enough evidence supporting the same [5]. The baby may acquire infection while passing through the birth canal as it comes in contact with the infected body fluids of the mother and during handling of the baby by infected personnel [5]. Common presentations of COVID-19 infection in neonates are fever, respiratory distress, poor feeding, gastrointestinal symptoms, shock, cardiac involvement, mucocutaneous inflammation, irritability, and lethargy [5]. In addition, MIS-C in neonates may lead to coagulopathies, coronary artery dilatation, and neurological manifestations [6], as was observed in our case. MIS-C is a potentially life-threatening condition presenting with symptoms arising from inflammation of various organs and systems of the body. The case definition of MIS-C was first given by the WHO [7].

MIS-C is less likely in neonates as their immune system is not developed. There have been a few case reports describing this condition [8-10]. It occurs due to cytokine storm as evidenced by the raised inflammatory markers. MIS-C is generally diagnosed in children 2–6 weeks after exposure to the virus. The possible mechanism of this condition occurring in a neonate less than a week old is the transplacental transmission of maternal IgG antibodies to COVID-19 which may be responsible for the hyperinflammatory cascade [9]. This is supported by case reports of neonates with MIS-C-like pictures showing excellent response to immunosuppression and IVIG [9]. This phenomenon in neonates can also be explained by fetal IRS (FIRS). FIRS is a local or systemic inflammatory response of the fetus to infectious or non-infectious stimuli which lead to clinical manifestations in postnatal life. IVIG may be beneficial in neonatal hyperinflammatory state according to the some case reports [9,11]. Some cases have also shown progressive improvement on methylprednisolone therapy [9]. Remdesivir inhibits viral replication and hence helps in reducing the duration of ventilator support and number of days

of hospitalization as was seen in our case. This is supported by case reports showing the therapeutic benefit of remdesivir in neonates with COVID-19 respiratory illness [12]. The safety and efficacy of the use of remdesivir in neonates are yet to be demonstrated in large-scale studies and clinical trials.

MIS in neonates can prove to be fatal, but the most studies on the same show favorable outcomes in adequately-treated neonates. Long-term follow-up data are limited. However, based on studies conducted in the pediatric population, there may be activity limitation and reduced exercise tolerance for around 3–6 months post-illness. Coronary artery abnormalities resolve by 6 months post illness [13].

CONCLUSION

Neonates fall into a grey area when it comes to symptomatology and reaching a definite diagnosis. They may demonstrate non-specific symptoms. The majority of neonates infected with COVID-19 will have no or mild symptoms. Those babies with more severe presentation comprise a handful of cases. Except for a few case reports, the term MIS-N is not yet widely recognized. The case definitions for MIS-C are still in the forming stages; neonates may not fulfill all the criteria but may still have hyperinflammatory syndromes. Babies born to COVID-19 positive mothers and who have severe symptoms not explainable by illnesses commonly affecting this age group should be thoroughly investigated for MIS-C. More studies are needed to establish proper guidelines for the management of affected neonates. Long-term follow-up studies are also needed to know the chronic and residual effects of COVID-19 infection at such an early age.

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