Case Report

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Multisystem inflammatory syndrome in a neonate secondary to COVID-19: a case report

Sristi Upadhyay, MD[a], Sagar Devkota, MD[b,*]

Introduction and importance: Multisystem inflammatory syndrome in children secondary to coronavirus disease 2019 (COVID-19) (MIS-C) is very common and may present with clinical features similar to Kawasaki disease but is rarely reported in neonates (MIS-N). Any history of maternal upper respiratory tract infection should raise suspicion of MIS-N secondary to COVID-19 in critically ill neonates.

Case presentation: The authors present a term neonate with gradually progressive respiratory distress requiring mechanical ventilation with marked improvement after starting immunoglobulin and steroids after blood investigations revealed high IgG COVID-19 antibody titers.

Clinical findings and investigation: Admitted to the Neonatal Intensive Care Unit as he received bag and mask ventilation for 30 s following delivery, he was kept under oxygen via nasal prongs; but he still had nasal flaring, subcostal retraction, and tachypnea. All the blood investigations were within normal limits except for elevated C-reactive protein.

Intervention and outcome: With no improvement despite oxygen via nasal prongs, he was kept under bubble continuous positive airway pressure with positive end-expiratory pressure of 5 cm of H_2O. With no improvement even after 24 h of noninvasive ventilation, he was kept under mechanical ventilation in assisted pressure-controlled mode with a peak inspiratory pressure of 22 cm H_2O and respiratory rate of 40 breaths/minute. As the mother gave a history of on-and-off cough for almost a month, samples were sent for COVID-19 antibodies which came out to be positive with very high titers of IgG antibodies. Intravenous steroids, immunoglobulin, and subcutaneous low molecular weight heparin were started and marked improvement was noted. The peak inspiratory pressure and FiO_2 were gradually tapered off, and he was extubated on the 10th day of mechanical ventilation.

Conclusion: Multisystem inflammatory syndrome in neonates is rare but should always be considered in neonates with multisystem involvement and a history of maternal upper respiratory tract infection after excluding all other causes.

Keywords: COVID-19, multisystem inflammatory syndrome, neonate

Introduction

Despite the increasing number of cases of multisystem inflammatory syndrome in children (MIS-C) secondary to coronavirus disease 2019 (COVID-19) infection, it has rarely been reported in neonates (MIS-N)[1]. It is thought to be secondary to dysregulated immune response following exposure to COVID-19[2]. The perinatal transfer of COVID-19 infection from the mother has been implicated as the pathogenesis in the majority of the cases[3].

The diagnosis of MIS-N requires a history of maternal COVID-19 infection with high titers of antibodies in neonates with involvement of two or more organ systems with no other alternate diagnosis[4] (Table 1).

We present a newborn with bilateral pneumonia under mechanical ventilation with very high titers of IgG antibodies for COVID-19 and abdominal distention with a maternal

HIGHLIGHTS

- Multisystem inflammatory syndrome in newborns is rarely reported.
- It may mimic Kawasaki disease, which may lead to diagnostic delay.
- It should be considered in any critically ill neonate with a maternal history of suspected COVID-19.

[a]Department of Pediatrics and Adolescent Medicine and [b]Department of Anesthesiology and Intensive Care, Kulhudhuffushi Regional Hospital, Kulhudhuffushi, Maldives

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*Corresponding author. Address: Kulhudhuffushi Regional Hospital, 02110 Kulhudhuffushi, Maldives. Tel.: +960 993 1620. E-mail: sagar_1dev@yahoo.com (S. Devkota).

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Table 1

Diagnostic criteria for neonatal multisystem inflammatory syndrome (MIS-N).

(1) A neonate aged <28 days at the time of presentation
(2) Laboratory or epidemiologic evidence of SARS-CoV-2 infection in the mother
  (a) Positive SARS-CoV-2 testing by RT-PCR, serology (IgG or IgM), or antigen during pregnancy
  (b) Symptoms consistent with SARS-CoV-2 infection during pregnancy
  (c) COVID-19 exposure with confirmed SARS-CoV-2 infection during pregnancy
  (d) Serological evidence (positive IgG specific to SARS-CoV-2 but not IgM) in the neonate
(3) Clinical criteria
  (a) Severe illness necessitating hospitalization AND
  (b) Two or more organ systems affected [i.e. cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, neurological, temperature instability (fever or hypothermia)] OR
  (c) Cardiac AV conduction abnormalities OR coronary dilation or aneurysms (without the involvement of a second organ system)
(4) Laboratory evidence of inflammation. One or more of the following: an elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH, or IL-6; elevated neutrophils or reduced lymphocytes; low albumin
(5) No alternative diagnosis (such as birth asphyxia – cord pH 7.0 and Apgar score 3 at 5 min; viral or bacterial sepsis – confirmed blood culture; maternal lupus resulting in neonatal AV conduction abnormalities; presence of these findings indicating an alternate diagnosis) excludes MIS-N

AV, atrioventricular; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IgG/M, immunoglobulin G/M; IL-6, interleukin-6; LDH, lactate dehydrogenase; MIS-N, multisystem inflammatory syndrome in neonates; RT-PCR: reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

history of upper respiratory tract infection who improved after initiation of immunoglobulin and steroids.

Case presentation

A term neonate delivered via elective cesarean section weighing 3.2 kg was admitted to the neonatal intensive care unit for observation as he did not cry immediately after birth and received bag and mask ventilation for 30 s with a diagnosis of respiratory distress secondary to early onset neonatal sepsis. Following bag and mask ventilation, he cried but had tachypnea and subcostal retraction. Oxygen via nasal prongs was started, but there was no improvement; he was kept under a bubble of continuous positive airway pressure (CPAP) with positive end-expiratory pressure (PEEP) of 5 cm H_2O. There was increase in respiratory distress despite 24 h of noninvasive ventilation with arterial blood gas analysis revealing hypoxemia and hypercapnia. His chest radiograph revealed bilateral diffuse infiltrates suggestive of bilateral pneumonia (Fig. 1). Blood and urine cultures were negative. Based on these findings, endotracheal intubation was done, and he was kept under mechanical ventilation with assisted pressure-controlled mode, and antibiotics were upgraded. He was stable under mechanical ventilation but required high peak inspiratory pressure (P_{insp}) and fractional oxygen concentration (FiO_2) to maintain saturation. On the 4th day of life, he developed abdominal distension and had not passed stool for 48 hours; an abdominal radiograph was done, which revealed dilated bowel loops. Nasogastric decompression was done. Digital rectal stimulation was done, after which he passed stool. A stool for occult blood was also sent, which came negative. Abdominal distension gradually improved over 72 hs. Despite being on a mechanical ventilator for 7 days with high P_{insp} (up to 22 cm H_2O) and FiO_2, we were not able to taper the ventilator settings. So, further history was explored to rule out if we had missed anything in the beginning. After multiple interviews with the mother, she revealed that she had had on-and-off cough for about a month. High-resolution non-contrast computed tomography chest was also done, which revealed bilateral upper and lower lobe ground-glass opacification suggestive of neonatal pneumonia (Fig. 2). Echocardiography revealed normal biventricular function with no valvular abnormalities with minor collaterals to main pulmonary arteries. Based on these findings, we suspected COVID-19 infection in the mother and sent her blood sample for COVID-19 antibodies which came out to be positive (IgG). Blood samples of the neonate were also sent, which revealed very high titers of IgG antibodies (>2600 AU/ml) which confirmed our diagnosis, after which intravenous immunoglobulin (2 g/kg over 48 h), steroids (dexamethasone at 0.15 mg/kg per day) and low molecular weight heparin were started. Marked improvement was seen, after which we were able to taper the peak inspiratory pressure and FiO_2, and he was extubated on the 10th day of mechanical ventilation. After extubation, he was kept under nasal CPAP which was gradually tapered off. His blood investigations during the course of treatment are shown in Table 2.

Discussion

MIS-C in neonates, also known as MIS-N, is most likely secondary to maternal transmission of infection during the intrauterine period; however, this seems uncertain[5]. It has been rarely reported but should always be considered in critically ill neonates with a history of contact or maternal infection after excluding all other common causes. Neonate with MIS-N would present with varying degrees of multiorgan system involvement, and it is associated with significant morbidity and mortality[6].

The exact mechanism for the multiorgan involvement and the disease process has been poorly understood but is known to be distinct from the cytokine storm of severe acute COVID-19 as well as the inflammatory response as seen in Kawasaki disease along the autoantibody-mediated pathology[7]. The diagnosis of MIS-N in a newborn is always a challenge and requires vigilance as the clinical presentation usually mimics that of sepsis and other conditions associated with prematurity[8]. Clinical features may vary as compared to children and adults, but laboratory parameters like markers of inflammation may be supportive for evidence of inflammation and multisystem involvement[9]. Our patient had worsening respiratory distress requiring mechanical ventilation with elevated levels of C-reactive protein and radiological findings suggestive of neonatal pneumonia.

The management of MIS-N requires vigilant monitoring and immune modulators like immunoglobulin, steroids, and thromboprophylaxis[10]. As MIS-N is an inflammatory

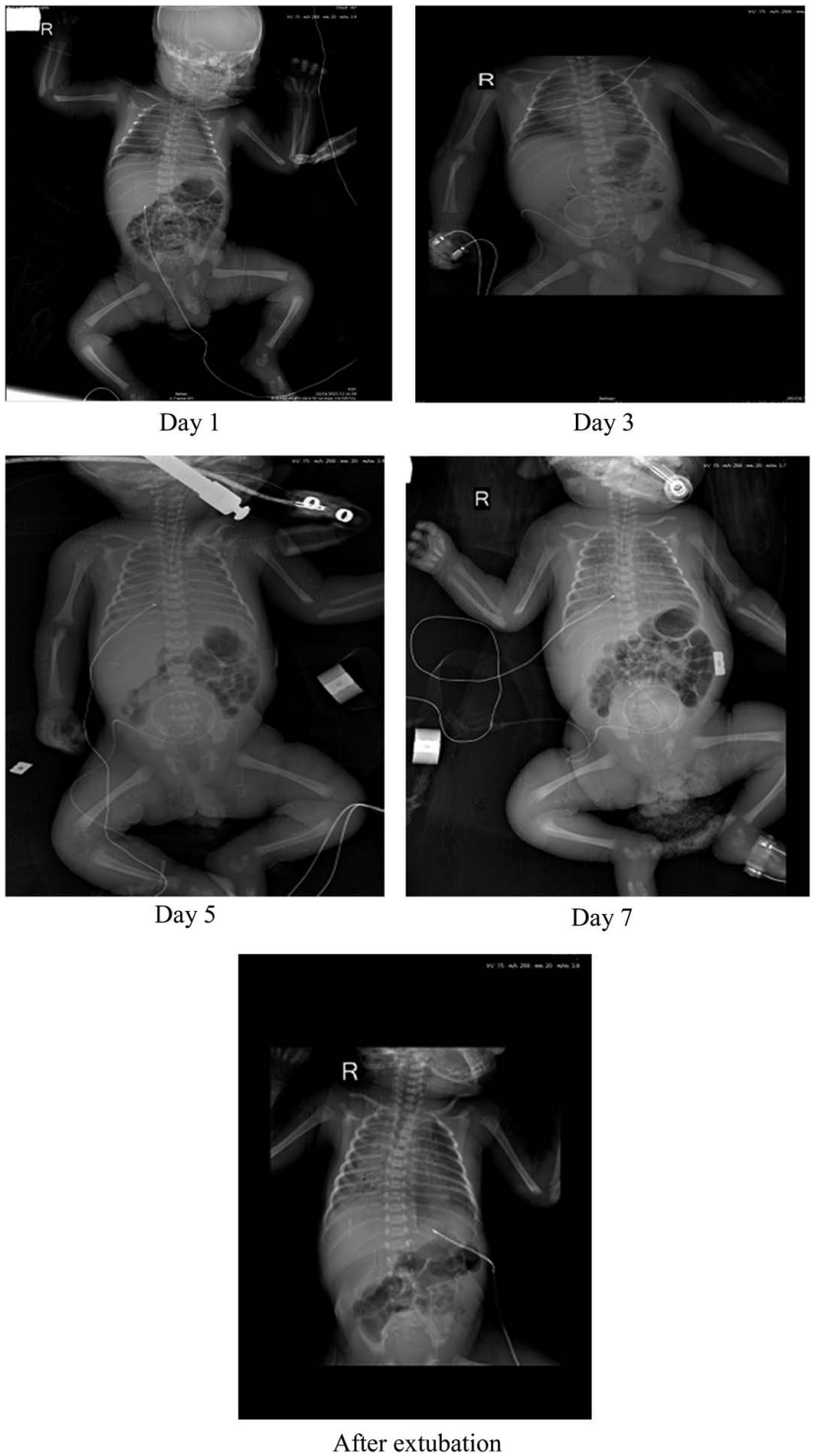

Figure 1. Serial chest radiographs (anteroposterior view) showing gradually improving bilateral pneumonia.

disorder, the use of antibiotics should be judicious[11]. In our case, the initial interview with the mother did not reveal any significant maternal history. With no improvement despite multiple antibiotics and mechanical ventilation, the second interview revealed on-and-off history of cough for about a month which prompted us to think in the line of MIS-N secondary to COVID-19. The high IgG antibody titers and improvement after starting immunoglobulin and steroids established the diagnosis of MIS-N.

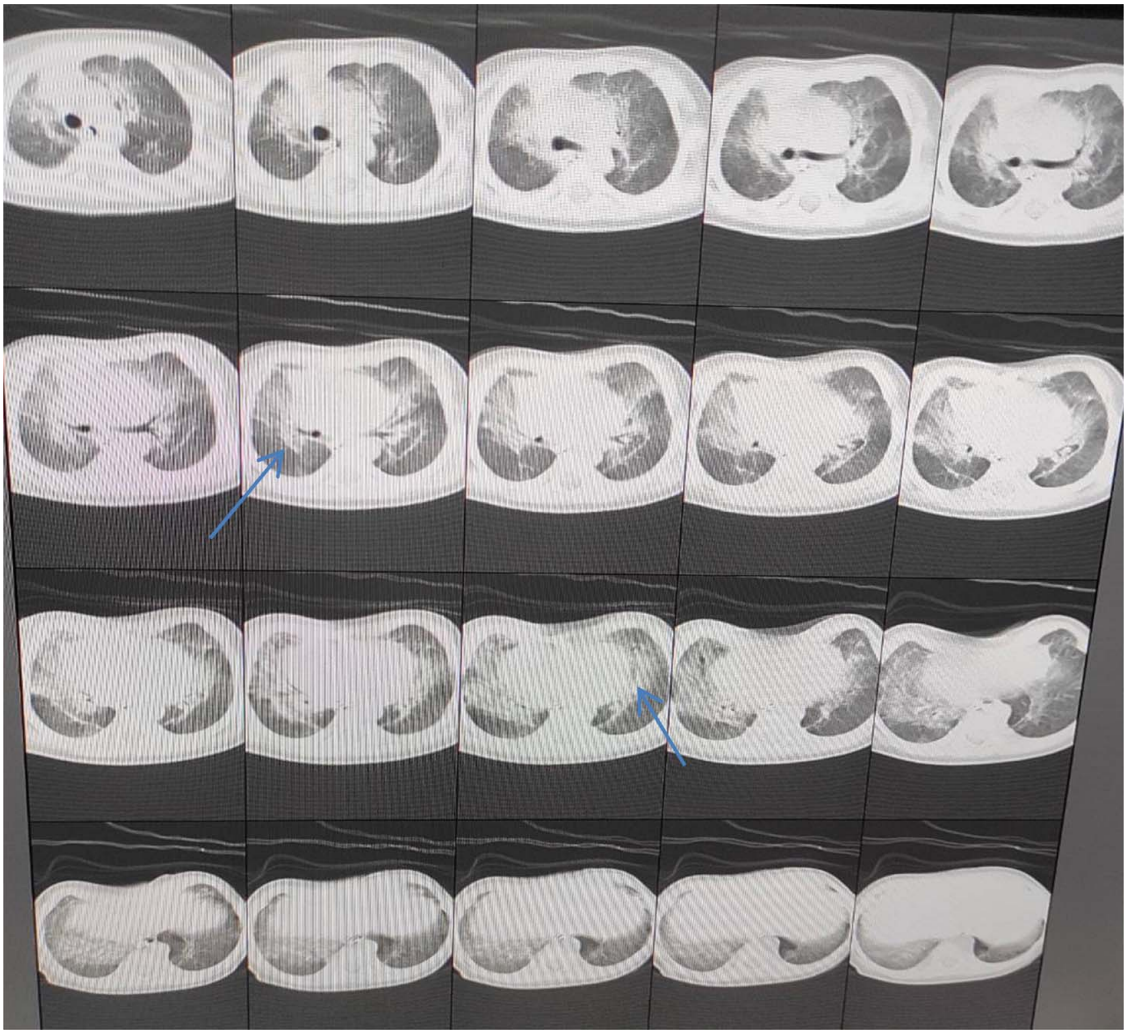

Figure 2. Computed tomography chest showing bilateral upper lobe air space opacification with air bronchogram inside, more noted on the right side along with lower lobe diffuse ground-glass attenuation suggestive of neonatal pneumonia (blue arrows).

Conclusion

Despite multisystem inflammatory syndrome being rare in neonates, any history of severe acute respiratory syndrome coronavirus 2 infection in mother or maternal contact with COVID-19 patients may potentially be associated with early neonatal multisystem inflammation, thrombosis, and atrioventricular conduction abnormalities. Therefore, MIS-N should always be considered in neonates with multisystem inflammation after excluding all other causes.

Table 2

Blood investigations.

	Admission	Day 3	Day 5	Day 7	Day 9	Day 11	Day 13
Hb (g/dl)	18	18	14.2	12.3	12.2	14	12.2
Total leukocyte count (per mm^3)	26 190	16 030	19 040	33 030	36 390	15 180	13 680
Neutrophil/lymphocytes	66/16	64/20	65/16	61/21	67/17	53.3/24/8	63/23
Packed cell volume	52.6	50.9	40	42	36	35	40
Platelets (per mm^3)	262 000	230 000	312 000	540 000	694 000	665 000	373 000
CRP	10.9	43.2	27.2	16.8	17	15.2	8.3
Urea/creatinine	18/0.8	29/1.0	13/0.6		6/0.70		10/0.8
Na/K	135/5.1	134/4.7	139/4.4		135/4.9		133/4.5

CRP, C-reactive protein; Hb, hemoglobin.

Ethical approval

Not applicable (a case report does not require ethical approval at our institute).

Consent

Written informed consent was obtained from the parents for the publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contributions

S.U. and S.D.: conceptualized the study; S.U.: was in charge of the case; S.U. and S.D.: reviewed and edited the manuscript.

Conflicts of interest disclosure

The authors declare that they have no conflicts of interest.

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