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Case Report

Neonatal Multisystem Inflammatory Syndrome (MIS-N): The First Case Report in Thailand

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Abstract: Cases of multisystem inflammatory syndrome in children (MIS-C-like disease), have rarely been reported in neonates. A 33-week gestational age twin B female neonate presented with respiratory distress, tachycardia, and abdominal distention at 15 days of age. Echocardiogram found reduced left ventricular ejection fraction to 33%. Cardiac enzyme levels were all elevated: creatine kinase-MB 6.1 ng/mL (normal 0–4.5 ng/mL), troponin-T 170 ng/L (normal < 14 ng/L) and NT-proBNP > 35,000 pg/mL (normal 250.0 to 3987.0 pg/mL). Multiplex PCR of nasopharyngeal swab material was negative for respiratory pathogens. Serological tests revealed negative anti-spike SARS-CoV-2 IgM but positive anti-nucleocapsid SARS-CoV-2 IgG in both the mother and the patient. The mother provided a history of COVID-19 during pregnancy at 19 weeks gestation. The patient was diagnosed with neonatal multisystem inflammatory syndrome (MIS-N) and successfully treated with intravenous immunoglobulin (two doses of 1 gm/kg/dose) and methylprednisolone (2 mg/kg/day for 5 days then tapered off). She later developed coronary vessel (LMCA and RCA) dilation. The non-identical twin A did not develop MIS-N, suggesting a role of host genetic background. Newborn infants born to SARS-CoV-2-infected mothers at any time during pregnancy should be closely monitored for MIS-N. The optimal treatment approaches to this syndrome and the prognosis require further study.

Keywords: neonatal; MIS-N; MIS-C; SARS-CoV-2; COVID-19

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1. Introduction

Since 2019, SARS-CoV-2 infection and the resulting global COVID-19 pandemic have imposed a significant burden on the public health system. As of 14 August 2022, the WHO has reported 587 million confirmed cases and 6.4 million deaths worldwide [1]. Although disease severity is generally much lower in pediatric populations compared to adults, reports have emerged of a multisystem inflammatory syndrome in children (MIS-C) occurring four to six weeks after SARS-CoV-2 infection [2]. However, evidence of MIS-C in neonates is still limited. Pawar et al. and More et al. recently reported a case series of an MIS-C-like disease in neonates, termed MIS-N [3,4]. We present the first case report of MIS-N in Thailand, in a premature neonate who developed respiratory distress and abdominal distention at 15 days of life (DOL).

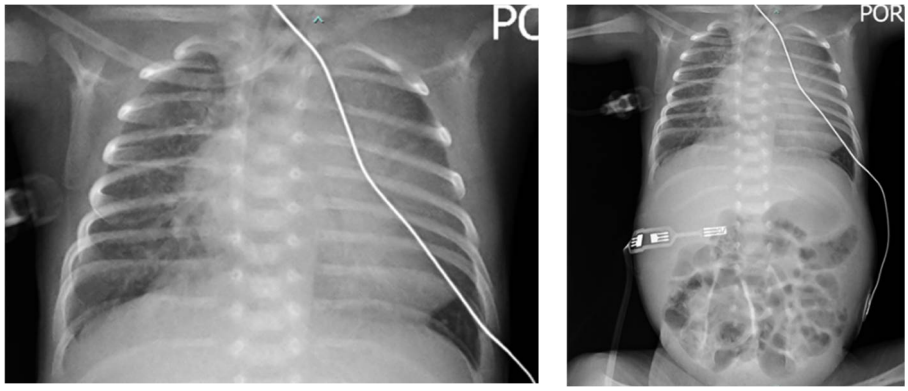
2. Case Presentation

A preterm 33-week gestational age twin B female infant weighing 1230 g was delivered by emergency Caesarean section during threatened preterm labor with selective fetal growth restriction due to monochorionic diamniotic twin pregnancy. The twins required no resuscitation and Apgar scores were 9 and 10 at 1 and 5 min, respectively. They were born to

a 34-year-old mother with a history of asymptomatic COVID-19 at gestational age 19 weeks. The mother denied any history of SARS-CoV-2 reinfection or COVID-19 vaccination during pregnancy. Nasopharyngeal swab for SARS-CoV-2 PCR of the mother shortly before delivery was negative. Female twin A, weighing 1940 g, developed tachypnea at 6 h of life, was diagnosed with transient tachypnea of the newborn, and required continuous positive airway pressure (CPAP) for 1 day before recovering for discharge at 3 DOL.

After delivery, twin B had poor suckling due to prematurity and received feeding via orogastric tube without signs of feeding intolerance. At 6 DOL, twin B developed abdominal distention with bilious return from the orogastric tube, and a new grade 1 systemic ejection murmur at the left parasternal border. A workup for late-onset neonatal sepsis including lumbar puncture was performed, intravenous cefotaxime plus amikacin were started empirically, and feeding was discontinued. Two days later, the clinical condition had improved and feeding was successfully restarted. At 10 DOL, twin B developed apnea and was treated with CPAP 5 cmH_2O, FiO_2 0.21 for suspected apnea of prematurity. All cultures were reported as no growth and antibiotics were discontinued after 7 days of treatment.

At 15 DOL, twin B developed new onset of desaturation with respiratory distress. Her vital signs revealed tachycardia (HR 170–180/min) and tachypnea (RR 70–80/min) without fever. The cardiac systolic ejection murmur at left parasternal border became louder, but without bounding pulse. Intravenous cefotaxime and amikacin and respiratory support (CPAP 6 cmH_2O, FiO_2 0.3–0.4) were resumed. The chest X-ray revealed marked cardiomegaly with an enlarged pulmonary trunk. The abdominal X-ray showed mild dilation of the small and large bowel with no evidence of necrotizing enterocolitis (Figure 1A,B). Because of the presence of multiorgan system involvement with significant cardiovascular manifestations and maternal history of COVID-19, MIS-N was suspected.



(**A**) (**B**)

Figure 1. Chest X-ray and abdominal X-ray on day 15 of life showed: (**A**) marked cardiomegaly with enlarged pulmonary trunk but minimal pulmonary infiltration; (**B**) mild dilation of small and large bowel without evidence of necrotizing enterocolitis.

The complete blood count, serum electrolytes, and inflammatory markers (C-reactive protein, procalcitonin, and fibrinogen) were normal and results of blood cultures were negative. A lumbar puncture was not performed because of clinical instability. EKG showed no abnormalities. Echocardiography showed a small perimembranous ventricular septal defect, mild coarctation of the aorta, and moderate-to-severe tricuspid regurgitation. The left ventricular ejection fraction (LVEF) was reduced to 33%. No coronary artery abnormalities were noted. Cardiac enzyme levels were all elevated: creatine kinase-MB 6.1 ng/mL (normal 0–4.5 ng/mL), troponin-T 170 ng/L (normal < 14 ng/L) and NT-proBNP > 35,000 pg/mL (normal 250.0 to 3987.0 pg/mL) [5], suggesting heart failure with clinical manifestation likely from myocarditis. PCR of nasopharyngeal swab material was negative for respiratory viruses and enterovirus 71. The stool PCR for enterovirus 71 was also negative. The nasopharyngeal swabs for SARS-CoV-2 PCR in both mother and infant were negative. Serological tests revealed negative anti-spike SARS-CoV-2 IgM but

positive anti-nucleocapsid SARS-CoV-2 IgG in both the mother and infant twin B. Other inflammatory markers were elevated: ferritin 912 ng/mL (normal 25–200 ng/mL), D-Dimer 31,191 ng/mL (normal 500 ng/mL), LDH 989 U/L (normal 225–600 U/L), and interleukin-6 14.69 pg/mL (normal 0–7 pg/mL).

MIS-N was diagnosed and two doses of intravenous immunoglobulin (1 gm/kg/dose, total 2 gm/kg) were initiated on DOL15. Left ventricular failure was treated with inotropes (intravenous dobutamine 9 mcg/kg/min, intravenous milrinone 0.1 mcg/kg/min) and diuretics (intravenous furosemide 0.5 mg/kg/dose every 8 h plus oral spironolactone 2 mg/kg/day). After IVIG treatment, follow-up echocardiography showed improved LVEF to 44%; coronary artery dilation (by Montreal parameter) was noted in the LMCA (diameter 1.8 mm, Z-score 3.34), and proximal RCA (1.3 mm, Z-score 2.22). Intravenous methylprednisolone (2 mg/kg/day) was started on DOL 20. As the cranial ultrasound showed intraventricular hemorrhage grade I, enoxaparin for thrombosis prevention was not given.

Twin B responded well to treatment. After 5 days, methylprednisolone was reduced to 1 mg/kg/day and subsequently tapered off. Respiratory support and supplemental oxygen were discontinued, inotropic support and intravenous antibiotics were discontinued after 12 days of treatment, and full enteral feeding was resumed on DOL 26. The cardiac and inflammatory markers at 2 weeks after IVIG treatment declined: creatine kinase-MB 7.66 ng/mL, troponin-T 233 ng/L and NT-proBNP > 27,231 pg/mL, and interleukin-6 4.98 pg/mL. Follow-up echocardiogram revealed normalized LVEF of 81%, but coronary artery dilation was persistent: LMCA diameter 2.2 mm (Z-score 4.81), LAD 1.5 mm (Z-score 3.22), and RCA 1.6 mm (Z-score 3.34). Repeat cranial ultrasound showed no intraventricular hemorrhage and aspirin 5 mg/kg/day was initiated and continued for 6 weeks. Echocardiography after 6 weeks of aspirin treatment showed regression of coronary artery dilatation, with LMCA diameter 1.2 mm (Z-score 0.95), LAD 1.3 mm (Z-score 1.92), RCA 0.8 mm (Z-score 1.04), and LVEF of 70%. She had oromotor dysfunction from prematurity which slowly resolved, and was discharged from the hospital on DOL 86. Twin A remained healthy, and, interestingly, anti-SARS-CoV-2 nucleocapsid IgG tested on DOL 20 was negative.

3. Discussion and Conclusions

MIS-N is a newly recognized syndrome occurring in neonates born to mothers with SARS-CoV-2 infection during pregnancy. In critically ill neonates presenting with multiorgan dysfunction, particularly with cardiovascular manifestations such as myocarditis, shock, or arrhythmia, MIS-N should be considered in the differential diagnosis. In this case the diagnosis was pursued due to clinical refractory multisystem organ involvement including myocarditis, ventricular failure, and pathological coronary artery dilation with temporal association of maternal COVID-19 infection, and positive neonatal anti-SARS-CoV-2 antibody. As the patient did not respond to standard medical therapy, and there was no other disease that could explain the clinical course, the regression of coronary artery dilation by intravenous methylprednisolone strongly supported the diagnosis of MIS-N. We believe this is the first case of MIS-N ever reported in Thailand. We suggest that in ill neonates born to mothers with COVID-19 infection, echocardiogram should be performed to look for coronary artery dilation and/or ventricular dysfunction, and treatment with IVIG and/or steroids in suspected cases of MIS-N should be considered.

Newborns may develop MIS-C and MIS-N with either SARS-CoV-2 infection or maternal acquired antibodies [3,4,6–12]. Published reports indicate that SARS-CoV-2 can persist in mothers and infect the fetus where SARS-CoV-2 infection and multisystem inflammation occur in the same subject [6,7]. In this report, twin B may have experienced a SARS-CoV-2 infection in utero or only received passive transfer of maternal antibodies; however, the anti-spike SARS-CoV-2 IgM was negative, making it less likely to be an in utero infection.

Several institutions have offered diagnostic criteria for MIS-C, including the Royal College of Paediatrics and Child Health, Centers for Disease Control and Prevention (CDC),

and the WHO [13,14]. However, there has been no international consensus criteria for the diagnosis of MIS-N. Pawar [3] suggested that MIS-N is a unique phenomenon induced by passive transfer of maternal antibodies in the setting of COVID-19 in pregnancy, leading to multisystem inflammation. The symptom onset of twin B was about 15 weeks after the initial maternal SARS-CoV-2 infection, similar to the case series of MIS-N which suggested that symptoms may present 2–20 weeks (median 6 weeks) after infection [3]. A systematic review of 16 reports of MIS-N revealed that only 65% (30/46) had elevated C-reactive protein (CRP) and there were high levels of troponin-T in all neonates (8/8) who were tested [9]. This is distinct from neonatal MIS-C from direct SARS-CoV-2 infection of the infant in the perinatal period leading to MIS-C 2–4 weeks later where the CRP level is always significantly elevated. Identifying SARS-COV-2 infection in infants is the key criterion differentiating MIS-C from MIS-N. It was less likely that twin B acquired a SARS-CoV-2 infection post birth resulting in MIS-C (as opposed to MIS-N) because of the negative PCR for SARS-CoV-2 and the onset of symptoms as early as 6 days of age.

The mechanisms of MIS-N are presently unknown. Multi-organ dysfunction in MIS-N is very similar to that seen in MIS-C [13], and could be explained by dysregulated immune responses to passive transferred maternal antibodies resulting in downstream cytokine-mediated inflammation. It is of interest that twin A did not develop MIS-N and had undetectable maternal anti-SARS-CoV-2 nucleocapsid antibody; twin A and B are non-identical, suggesting that host factor background may also play a role in the development of this syndrome. MIS-C and MIS-N have similar clinical manifestations, but the prognoses of these two syndromes remain to be defined. There is currently little direct evidence that IVIG and steroid treatment are beneficial in MIS-N. However, the clinical utility of these treatments extrapolated from observations in older children with MIS-C appeared helpful in this patient. IVIG, methylprednisolone, and aspirin are the potential management options for Kawasaki disease treatment. The characteristics of MIS-C and MIS-N suggest that both are Kawasaki disease-like and are associated with the SARS-CoV-2 virus [15,16]. MIS-N and MIS-C may be driven by viral activation of immune cells via Fc receptors. This provides a basis for the clinical benefit of IVIG, which may inhibit antibodies bound to Fc receptors. Treatment with methylprednisolone targets immune cells and aspirin is a known mast cell stabilizer and COX inhibitor, which are the effective treatment components. The etiologic role of transplacental antibodies and/or mediators of inflammation and heritable host factors in causing MIS-N, as well as optimal treatment approaches to this syndrome, require further study [3,4,13,14].

In conclusion, multisystem inflammatory syndrome in neonates could be the consequence of perinatal infection resulting in MIS-C or acquisition of maternal antibodies resulting in MIS-N. Infants born to mothers with a history of COVID-19 may have some protection against COVID-19 and MIS-C, but are still at risk for MIS-N. Newborn infants born to SARS-CoV-2-infected mothers at any time during pregnancy should be closely monitored for MIS-N and receive empirical treatment. Further studies are needed to define the appropriate treatment and understand the prognosis.

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