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CASE REPORT

# MULTI-SYSTEM INFLAMMATORY SYNDROME IN NEONATE (MIS-N) PRESENTING AS BOWEL OBSTRUCTION: A CASE REPORT

*Catherine Uy Cano, MD,[1] Lynard Anthony De Dios Ignacio, MD, FPPS,[1] Edwin Vasquez Rodriguez, MD, FPPS,[1] Froilan Vicente Gallardo Vinuya, MD, FPPS,[1] Robert Dennis J. Garcia, MD, MHSA[1,2] and Josefino Averilla Regalado, MD, FPPS[1]*
*[1]Department of Pediatrics, Cardinal Santos Medical Center, [2]Department of Pediatrics, Makati Medical Center*

## ABSTRACT

**Background:** Since the start of SARS-CoV-2 pandemic, a post-infection hyperinflammatory process in children with features similar to Kawasaki disease, termed multisystem inflammatory syndrome in children (MIS-C),[1] was identified. Thousands of MIS-C cases have already been reported worldwide.[2] As possible cases of MIS-C in neonates were increasingly identified, multisystem inflammatory syndrome in neonates (MIS-N) as a distinct entity was proposed as neonates may not manifest all the typical features described in older children.

**Case Presentation:** We describe the case of a previously well term neonate with sudden signs of bowel obstruction who later had multisystem involvement (cardiac, gastrointestinal, and hematologic). The baby was born to a 23-year-old multigravida with an unremarkable prenatal history except for COVID-19 infection during her 34$^{th}$ week age of gestation. The mother presented with mild respiratory symptoms and resolved with supportive management. Our patient was born stable, then had sudden manifestations of feeding intolerance on the 16$^{th}$ day of life and upon work-up had moderate anemia, elevated inflammatory and cardiac markers, ileus, and dilatation of proximal left coronary artery. RT-PCR for SARS-CoV2 was negative. The baby was managed with intravenous immunoglobulin (IVIG) and steroids, with rapid clinical and laboratory parameters improvement thereafter.

**Conclusion:** MIS-N is still evolving as a disease entity with no clear, directed guidance yet on diagnosis and management. Management is extrapolated from treatment of MIS-C. Additional case reports and series are warranted to increase awareness and enable better understanding of the disease pathology among clinicians for timely investigation, diagnosis, and management.

**KEYWORDS:** *Neonatal, Multi-System Inflammatory Syndrome (MIS-N), SARS-CoV-2, Case Report*

Correspondence:
Dr. Catherine U. Cano
Email: caihong14pchs@gmail.com

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## INTRODUCTION

Since the start of SARS-CoV-2 pandemic, a post-infection hyperinflammatory process in children with features like Kawasaki disease was identified. The disease process is labelled as multisystem inflammatory syndrome in children (MIS-C), defined by the US Centers for Disease Control and Prevention as a disease entity of sufficient severity to warrant hospitalization in individuals < 21 years, characterized by the presence of fever, laboratory evidence of inflammation and multisystem organ dysfunction, with temporal association to recent SARS-CoV-2 infection, and absence of other plausible alternate diagnoses.[1] Thousands of MIS-C cases have already been reported worldwide.[2] As possible cases of MIS-C in neonates were increasingly identified, multisystem inflammatory syndrome in neonates (MIS-N) as a distinct entity was proposed, as neonates may not manifest all the typical features described in older children. To date, there are eight case reports[2-9] and two case series[10-11] on neonatal multisystem inflammatory syndrome published, with various case inclusion criteria adapted from the CDC definition of MIS-C and modified to account for the mode of disease acquisition and physiology (i.e., underdeveloped pyretic response) unique among neonates. Majority of the neonates described were symptomatic within the first week of life and presented predominantly with respiratory or cardiac involvement. In this report, we describe the case of a 16-day old previously well term neonate with sudden signs of possible bowel obstruction, later noted to have multisystem involvement and managed as a case of MIS-N.

## CASE PRESENTATION

A singleton male infant was born to a 23-year-old G2P1 (1001) non-smoker and non-alcoholic beverage drinker on her 39 1/7 weeks AOG via repeat caesarean section.

The mother had COVID-19 infection confirmed via COVID-19 RT-PCR at 34 weeks AOG with mild respiratory symptoms, and was managed with Vitamin C + Zinc for two weeks and home isolation for 10 days. She completed two doses of COVID-19 vaccination prior to her illness. There was no maternal history of hypertension, diabetes mellitus, and bacterial or fungal infection. HBsAg, VDRL, and HIV tests were all non-reactive. The mother had regular intake of vitamins with no exposure to any teratogen or radiation. The baby was born live, term, singleton male, via repeat caesarean section, with APGAR score of 9 and 9, Ballard score of 39 weeks, with birthweight of 3355g (7 lbs 6 oz), birth length of 49.5cm, and was assessed as being appropriate for gestational age. He was discharged stable with the mother on the second hospital day, with good cry and good latch, jaundice up to the chest, and with adequate urine output and bowel movement within the first 24 hours of life. Since the baby was asymptomatic at birth, RT-PCR for SARS-CoV2 was not indicated. The newborn hearing screening and critical congenital heart disease screening results were normal. At home, the baby tolerated direct breastfeeding, but was started on mixed feeding on the 8th day of life due to inadequate maternal breastmilk supply. There was adequate urine output and bowel movements, with no hypothermic or hyperthermic episodes, no rapid progression of jaundice, and no jitters nor cyanosis noted. Newborn screening results later came back normal. Family history revealed hypertension, diabetes mellitus, and colon cancer on the paternal side. Social and environmental histories were non-contributory. He was taken cared for by both parents who were both fully immunized with COVID-19 vaccines and were asymptomatic. There was no travel history for the family since the baby was discharged from the hospital.

On the 16th day of life, the baby was noted to be pale-looking, with no signs of overt bleeding, with one hyperthermic episode (temperature of 38$^{o}$C). The baby also started having postprandial vomiting of initially brownish and, later, bilious in colour.

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Upon arrival at the ER, the baby was awake with fair cry and activity, and with good suck on gloved finger. He was thermoregulated at 36.5°C, HR was at 145 bpm, RR was at 48 cpm, and oxygen saturation at 98% at room air. There was generalized pallor, no rash, and no swelling nor erythema of the palms and soles. The baby had flat fontanelles and no conjunctival injection, lips were slightly pale and dry, buccal mucosa was moist, and there was no strawberry tongue. There were no signs of respiratory distress. Cardiac examination revealed distinct regular heart sounds with no murmur. Abdomen was soft, non-distended, with normal bowel sounds and no palpable mass nor organomegaly. Pulses were full and equal, and there was no peripheral cyanosis. Neurologic examination was essentially unremarkable. The admitting impression was late-onset neonatal sepsis versus Multisystem Inflammatory Syndrome in Neonate (MIS-N), given the history of maternal COVID-19 infection during late pregnancy, to rule out bowel obstruction. On admission, the baby was kept on nothing per orem and intravenous (IV) fluids were started. Orogastric tube (OGT) was inserted and yielded 40ml of bilious fluid. Capillary blood sugar (CBG) was normal. Nasopharyngeal swab for COVID-19 RT-PCR showed negative results. Complete blood count (CBC) showed decreased hemoglobin, normal WBC count, and thrombocytosis (see Table 1). Abdominal radiograph showed an impression of adynamic ileus (see Figure 1A and 1B). Electrolyte levels were normal. Antibiotics (cefotaxime and amikacin) were started. D-dimer, CRP and CPK-MB were more than 3x elevated while Pro-BNP was 15x elevated than normal and Troponin-I showed high risk results (see Table 1). Procalcitonin level was normal. The unexplained anemia with no identified source of bleeding prompted further work-up. Corrected reticulocyte count was normal and peripheral blood smear showed decreased and normocytic and normochromic RBC with some anisopoikilocytosis. There was normal WBC with lymphocytic predominance and increased platelet count.

Packed RBC transfusion (10ml/kg) was ordered to correct the anemia; however, a major incompatibility with the same blood type (blood type A+) was found, despite negative direct and indirect Coomb's test results. Compatible packed RBC of blood type O+ was later transfused with no untoward events. 2-D echocardiogram revealed proximal left coronary artery dilatation with a maximal intra-luminal diameter of 0.20cm, good left ventricular systolic and diastolic functions (ejection fraction of 68%), normal pulmonary arterial pressure and no pericardial effusion (see Figure 2). 15L-ECG revealed normal sinus rhythm with probable right ventricular hypertrophy (see Figure 3). Chest radiograph showed clear lungs with no cardiomegaly. Despite the presence of spontaneous bowel movements and being on NPO, there was persistence of bilious output per OGT. Repeat abdominal radiograph was done the next day showing no significant change in ileus (see Figure 1C and 1D). The diagnosis of MIS-N was made on day 2 of hospitalization, and intravenous immunoglobulin (IVIG) (2gm/kg/dose), IV methylprednisolone (2mg/kg/day, every 12 hours) and IV omeprazole were started. Urinalysis was negative for urinary tract infection, but urine culture grew 10,000 colony-forming units/ml of *Klebsiella pneumoniae* for which antibiotics were continued. OGT yielded minimal clear output on the 3rd to 4th hospital days. With the elevated D-dimer and 2-D echocardiogram findings, low dose acetyl-salicylic acid (ASA) (1.6mg/kg/day) was also commenced on the 4th hospital day as soon as feeding was started.

Post-IVIG and packed RBC transfusion, repeat laboratory tests done on the 5$^{th}$ hospital day showed improved hemoglobin and hematocrit, although still decreased as compared to the normal values for age. Leucocytosis, likely secondary to giving of steroids, along with reactive thrombocytosis were noted. Inflammatory and cardiac markers showed significantly decreased levels from the previous levels (see Table 1). Antibiotics were discontinued after three days as blood culture showed no growth.

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IV methylprednisolone was given for three days and was shifted to oral prednisone (1mg/kg/day), while IV omeprazole was shifted to oral esomeprazole. The baby was discharged stable on the 6th hospital day, tolerating expressed breastmilk, pinkish in color with good cry and activity.

He had adequate urine output and spontaneous bowel movements. Low dose ASA was continued and prednisone was tapered over four weeks. Esomeprazole was continued while he was on ASA and prednisone. The baby was scheduled for repeat 2D echo two months later that revealed normal results.

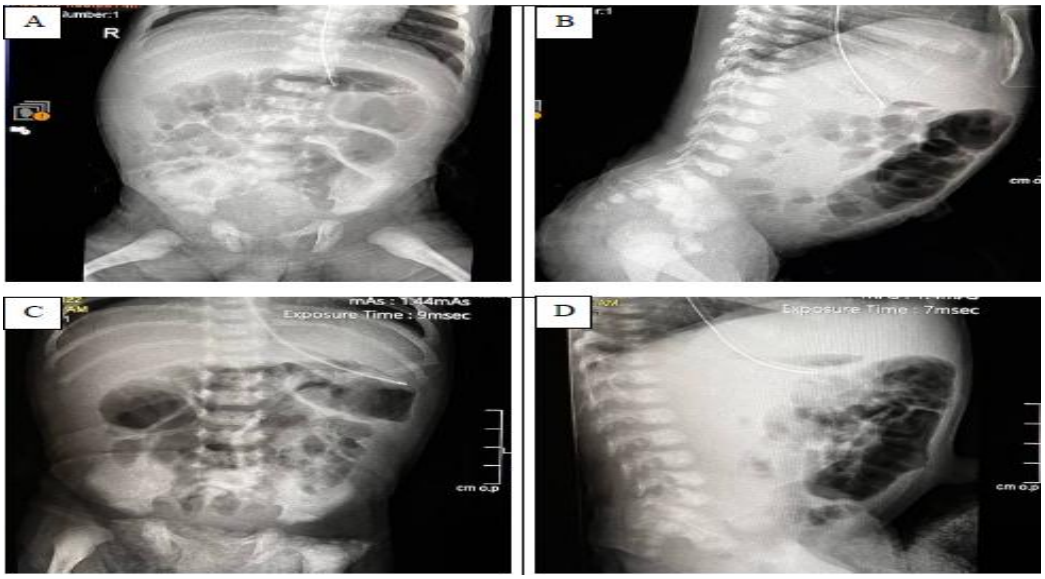


Figure 1. (A) and (B) Abdominal radiographs taken during first hospital day showed presence of gas-dilated loops of bowels, disorganized in pattern with no evidence of pneumoperitoneum. Impression: To consider adynamic ileus. (C) and (D) Abdominal radiographs on the second hospital day showed no significant change in the degree and number of gas filled bowel loops. Neither high-grade obstruction nor evidence of pneumoperitoneum was seen. Impression: No significant change in presumed ileus.

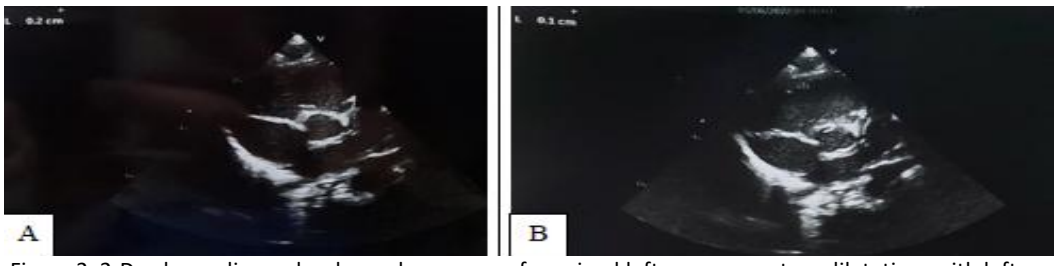


Figure 2. 2-D echocardiography showed presence of proximal left coronary artery dilatation, with left coronary artery measuring 0.20cm proximally (A) and 0.10cm distally (B).

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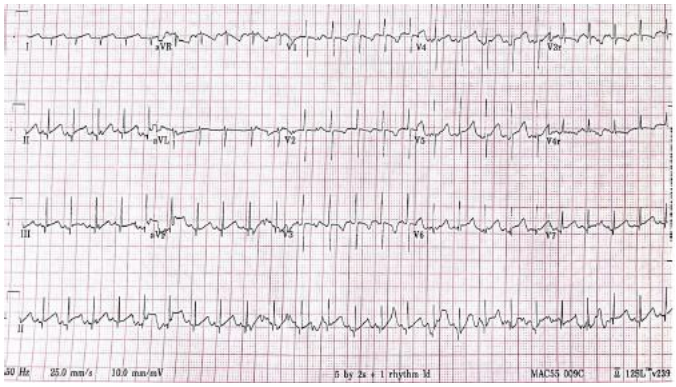

Figure 3. 15-Lead Electrocardiogram showed normal sinus rhythm and probable right ventricular hypertrophy.

Table 1. Laboratory Results

| Parameters | 1st HD | 2nd HD | 3rd HD | 4th HD | 5th HD |
|---|---|---|---|---|---|
| *CBC* | | | | | |
| Hgb*(g/dL)* | 10.2 (L) | 8.2 (L) | | | 11.6 (L) |
| Hct | 28 (L) | 22 (L) | | | 32 (L) |
| WBC*(10^9/L)* | 13.41 | 12.56 | | | 23.99 (H) |
| Neutrophil | 33 | 32 | | | 37 |
| Lymphocyte | 45 | 46 | | | 43 |
| Monocyte | 16 | 15 | | | 11 |
| Eosinophil | 7 | 7 | | | 8 |
| Basophil | 1 | - | | | 1 |
| Platelets *(10^12/L)* | 699 (H) | 648 (H) | | | 772 (H) |
| Reticulocyte count*(%)* | | 2.1 (1.1)* | | | |
| *Coomb's test* | | | | | |
| Direct | | | Negative | | |
| Indirect | | | Negative | | |
| *Electrolytes* | | | | | |
| Sodium*(mmol/L)* | 138 | | | | 135 |
| Potassium*(mmol/L)* | 5 | | | | 5.4 |
| Chloride*(mmol/L)* | 109 | | | | 111 |
| Calcium*(mmol/L)* | 2.51 | | | | 2.46 |
| *Inflammatory markers* | | | | | |
| CRP*(mg/L)* | 19.7 (3.9x↑) | | | | 2.1 |
| Procalcitonin*(ng/mL)* | | 0.21 | | | |
| LDH*(u/L)* | 243 | | | | |
| D-Dimer*(ng/mL)* | 1691.8 (3.3x↑) | | | | 656.4 (1.3x↑) |
| *Cardiac markers* | | | | | |
| CK-MB*(U/L)* | | 87 (3.5x↑) | | | 69 (2.8x↑) |
| ProBNP*(pg/mL)* | | 6781 (15x↑) | | | 1233 (2.7x↑) |
| Troponin I*(pg/mL)* | | 17.2 (↑risk) | | | 7.8 |
| *Kidney function* | | | | | |
| BUN*(mmol/L)* | | | | | 5.8 |
| Creatinine*(mg/dL)* | | | | | 0.33 |
| Urinalysis | Sp gr 1.005 Negative flow cytometry | | | | |
| Blood CS | Negative | | | | |
| Urine CS | ***Klebsiella Pneumoniae*** **10,000 colonies/ml** sensitive to Cefazolin, Ceftriaxone, Cefuroxime, Ciprofloxacin, Co-trimoxazole, Gentamicin, Nitrofurantoin, Piperacillin-tazobactam, resistant to Co-Amoxiclav | | | | |
| Peripheral blood smear | Normal white blood cell count with predominance of lymphocytes. Red blood cell count is decreased showing mostly normocytic, normochromic; few macrocytic, normochromic. Spherocytes (1+) and occasional elliptocytes are seen. Platelet count is increased. | | | | |
| COVID-19 RT PCR | Negative | | | | |

## DISCUSSION

The published literature regarding MIS-N is quite limited.[2-10] Majority of the reported cases presented with predominantly cardiac or respiratory involvement.[3-6,8-10] In the case series of Pawar, *et al.*, the gastrointestinal system was the third most common organ system involved in MIS-N, documented in 30% (6/20) of the neonates, after cardiac (90%, 18/20) and respiratory (55%, 11/20) systems.[9] Most of the reported cases of MIS-N were either symptomatic upon birth[3,4,6,8] or within the first week of life.[2,7,9,10] Our case shares some similarity with the MIS-N case reported by Kappanayil, *et al.* that described a late presenting term neonate who was initially born stable and fell suddenly ill on the 24th day of life.[5]

MIS-N was suspected in this neonate because of the mother's past history of COVID-19 infection seven weeks (34 weeks AOG) before the former developed fever. The diagnosis of MIS-N in our patient remains presumptive, made based on having a neonate with multi-organ dysfunction (cardiac, gastrointestinal, hematologic), following proven prenatal exposure to COVID-19, abnormal laboratory findings with dilated coronary artery on 2D echocardiography, elevated inflammatory markers and cardiac enzymes, and with a good response to immunomodulatory therapy. Neonatal Kawasaki Disease, with a high proportion of incomplete presentation in this age group, can be one plausible differential diagnosis to explain the coronary artery involvement, with anemia and thrombocytosis, which rapidly reversed with IVIG and corticosteroid therapy.[11] With the documented maternal COVID-19 during pregnancy and a prominent gastrointestinal manifestation, MIS-N was considered instead of neonatal Kawasaki disease.

By far, only three other cases of presumptive MIS-N were reported to have associated anemia.[6,8]

Shaiba, *et al.* described two preterms with presumptive MIS-N: a 36-weeker with anemia since birth, along with respiratory distress and cardiac involvement (moderately dilated left ventricle with poor systolic function, echogenic papillary muscles, widely patent ductus arteriosus with bidirectional shunt consistent with pulmonary hypertension, and elevated cardiac enzymes), and a 32-weeker with anemia on the 5th day of life, who also presented with respiratory symptoms upon birth, with elevated cardiac markers but normal 2D echo findings.[6] Malek, *et al.* reported a case of another late preterm (35-weeker) with presumptive MIS-N who likewise presented with respiratory distress and abnormal 2D echo findings (moderate persistent pulmonary hypertension, moderate perimembranous ventricular septal defect, small patent ductus arteriosus, and small atrial septal defect) upon birth, and was found with anemia on the 11th day of life. [8] Our patient had anemia on the 16th day of life, with feeding intolerance as the presenting symptom. The anemia worsened the next day without signs of overt bleeding.

Feeding intolerance has been reported in eight other cases.[2,3,9] Pawar, *et al.* described six neonates, of which two had brownish gastric aspirates, and two had lower gastrointestinal bleeding.[9] Aggrawal, *et al.* reported a 39-weeker who had nonbilious vomiting and abdominal distension on the 44th hour of life, along with respiratory symptoms and elevated cardiac markers, but normal 2D echo findings.[2] Borkotoky, *et al.* reported another term neonate (38-weeker) with the impression of persistent pulmonary hypertension upon birth, but who later (on the 14th day of life) presented with signs of early necrotizing enterocolitis with large aspirates pre-feed, increasing abdominal girth and vomiting.[3] Our patient presented with post-prandial vomiting on the first day of illness (16th day of life), with bilious OGT aspirate and findings of gas-dilated bowels with adynamic ileus in abdominal radiographs.

These gastrointestinal manifestations are more common in cases of multisystem inflammatory syndrome (MIS) compared to that of Kawasaki disease.

Ventricular dysfunction has been the most common 2-D echocardiographic finding in MIS-N reported in the literatures. [4-6,10] Our patient though had good left ventricular systolic and diastolic functions (EF 68% and FS 35%), but had proximal left coronary artery dilatation. Coronary artery dilatation or aneurysm was found in five other reported cases of presumed MIS-N.[4,7,9,10] In the case series of Pawar, *et al.*, all 20 neonates had cardiac involvement, with arrythmia as the most common cardiac abnormality found (44%, 11/20), followed by shock/cardiac dysfunction (20%, 5/10), and dilated coronaries were only found in two neonates (10%, 2/20).[9] Cardiac markers, when available, were all reported to be elevated.[2-6, 9-10] Our patient was found with highly elevated cardiac markers -- CK-MB, proBNP and Troponin I, upon work-up on the 17th day of life as soon as the impression of MIS-N was considered. ProBNP was 15 times elevated than normal prior to giving any medication.

To date, only a total of 33 cases of presumptive MIS-N were reported in the available literature (not including the *Possible* and *Unlikely MIS-N* cases from More, *et al.*). [2-10] Majority of the cases were managed with both IVIG and steroids with excellent response. [2-3,5-7,9-10] Our patient responded well to IVIG and steroids, with his clinical status and laboratory parameters remarkably improved thereafter.

To date, there is no clear, agreed case definition of MIS-N yet. Diagnostic criteria for MIS-N, as extrapolated from the CDC case definition for MIS-C, have been proposed (see Appendix A and B).[9,10] SARS-CoV-2 infection in newborns can be early-onset, secondary to vertical or intrapartum transmission, or late-onset, as acquired through close contact. [12-13]

Pawar, *et al.* differentiated MIS-N from MIS-C in neonates, defining MIS-N as multisystem inflammation in neonates secondary to maternal COVID-19 infection during pregnancy, thus involving two subjects (mother and neonate), while MIS-C in neonates refers to multisystem inflammation secondary to prior COVID-19 infection in the neonate, hence involving only one subject.[9] On the other hand, More, *et al.* identified MIS-N as multisystem inflammation in neonates with either maternal SARS-CoV-2 infection or previous neonatal SARS-CoV-2 infection.[10] In any case, our patient fulfilled these case definitions of MIS-N but most likely was due to maternal COVID-19 infection during pregnancy as our patient's RT-PCR for SARS-CoV2 was negative and he didn't have any symptoms of COVID-19 prior to this illness.

The exact etiopathogenesis of MIS-N is still being explored. Although vertical transmission of SARS-COV-2 infection has been reported in isolated cases, no conclusive evidence was found in a systematic review and meta-analysis of 39 studies involving 1316 women with SARS-COV-2 infection during pregnancy. [12,14-16] The limited expression of host membrane receptors for SARS-CoV-2 entry, namely angiotensin-converting enzyme (ACE) 2 and transmembrane protease serine 2 (TMPRSS2) in trophoblasts, was identified as a plausible reason to explain the low incidence of transplacental transmission of SARS-CoV-2 among term babies.[17] Efficient transplacental transfer of IgG antibodies has been well-documented.[18] These anti-spike IgG antibodies were speculated to be protective, similar to secretory IgA in breastmilk of COVID-19 vaccinated mothers, with no pathogenic role in MIS-N as they are not directed towards autoantigen.[9,19] Children though with MIS-C were found with elevated levels of antibodies against autoantigens (i.e., anti-SSB and anti-Jo-1).[19]

It is also postulated that autoantibodies against endothelial, gastrointestinal, and immune cells may have been produced in the maternal body after SARS-CoV-2 infection, and crossed the placenta to initiate MIS-N in genetically susceptible neonates, similar to how anti-SSA and anti-SSB cause rash and congenital heart block in neonates with neonatal lupus.[9] On the other hand, it is also speculated that the protective anti-spike IgG antibodies may cause autoimmune dysregulation in genetically susceptible newborns; these antibodies may bind to receptors on neutrophils and macrophages, leading to cytokine activation, which causes the various manifestations of MIS-N.[10]

There is lack of substantial evidence regarding the use of IVIG and corticosteroids in neonates, and its use in this age group has not yet been approved by the Food and Drug Administration (FDA). [2,4] Although available reports describing MIS-N have shown good clinical response to IVIG, with or without corticosteroids, the use of these drugs among neonates is not without risk; IVIG has been known to potentially cause necrotizing enterocolitis. [20] Immunomodulator therapy should be reserved for definitive cases, when indicated, to prevent overtreatment. In our patient, being symptomatic with laboratory abnormalities and maternal history of COVID-19, MIS-N was highly considered, thus the medical team decided to give IVIG and steroids. Luckily, our patient did not have any adverse events after medical treatments were given.

Since discharge, the baby remained stable and well, with consistent weight gain. Repeat 2D echo done upon follow up 2 months later showed normal findings with resolution of previously noted coronary artery dilatation. The baby was advised to continue exclusive breastfeeding, and to follow up for due vaccinations as well as regular paediatric well visits.

## CONCLUSION

We described a case of a previously well term neonate born to a mother who had COVID-19 at 34 weeks AOG, with sudden signs of bowel obstruction and eventual multisystem involvement (cardiac, gastrointestinal and hematologic). MIS-N was suspected in this neonate because of the mother's past history of COVID-19 infection seven weeks (34 weeks AOG) before the former developed fever. MIS-N is still evolving as a disease entity with no clear, directed guidance yet on diagnosis and management. A high index of suspicion for neonates of mothers with COVID-19 infection during pregnancy, and prompt diagnosis based on current available literatures, are keys to targeted management and better clinical outcomes. Additional case reports and series are warranted to increase awareness and enable better understanding of the disease pathology among clinicians for timely investigation, diagnosis and management of novel disease entities.

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This research received no external funding.

## CONFLICT OF INTEREST

None declared.

## INFORMED CONSENT STATEMENT

Informed consent was obtained from parents for the publication of the case.

## AUTHOR CONTRIBUTIONS

This case report was conceptualized by LADDI. CUC contributed to the literature search and manuscript preparation. LADDI, EVR, FVGV, RDG and JAR critically reviewed and edited the final manuscript.

All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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## APPENDIX A

**Proposed inclusion criteria for neonatal multisystem inflammatory syndrome (MIS-N) secondary to maternal SARS-CoV-2 exposure or infection by Pawar, *et al.* (2021)**

(1) A neonate aged <28 days at the time of presentation

(2) Laboratory or epidemiologic evidence of SARS-CoV-2 infection in the mother
- Positive SARS-CoV-2 testing by RT-PCR, serology (IgG or IgM), or antigen during pregnancy
- Symptoms consistent with SARS-CoV-2 infection during pregnancy
- Serological evidence (positive IgG specific to SARS-CoV-2 but not IgM) in the neonate

(3) Clinical criteria:
- Severe illness necessitating hospitalization AND
- Two or more organ systems affected [i.e., cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, neurological, temperature instability (fever or hypothermia)] OR
- Cardiac AV conduction abnormalities OR coronary dilation or aneurysms (without 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 $\leq$ 7.0 and APGAR score $\leq$ 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 alternative diagnosis excludes MIS-N).

**APPENDIX B**

**Proposed inclusion criteria for neonatal multisystem inflammatory syndrome (MIS-N) by More, *et al.* (2022)**

(1) Symptoms presenting from birth to the first four weeks of life
(2) Fever along with two or more systems involvement (fever, if present, is suggestive but not mandatory for diagnosis in the newborn)
(3) Evidence of raised inflammatory markers such as CRP, PCT, D Dimer, Ferritin, and IL-6
(4) Evidence of SARS-CoV-2 antibodies in the neonate (considered mandatory for a diagnosis of MIS) and SARS-CoV-2 antigen should be negative during the presentation to rule out active SARS-CoV-2 infection to support the immunological process

AND

Associated evidence of maternal SARS-CoV-2 infection, defined as either supporting history or laboratory (positive SARS-CoV-2 quantitative RT-PCR test in a nasopharyngeal sample during the peripartum period) or epidemiological evidence of infection in the form of SARS-CoV-2 antibodies (for confirming the transplacental mechanism of MIS-N)

OR

History of prior confirmed neonatal SARS-CoV-2 infection (for confirming mechanism of MIS-N due autoantibodies secondary to SARS-CoV-2 infection) which can be classified based on the type of SARS-CoV-2 transmission in neonates as per WHO criteria as follows:

(a) In utero transmission — nasopharyngeal swab at age <24 hours positive for SARS-CoV-2 and positive serology for SARS-CoV-2 IgM and IgG.
(b) Intrapartum transmission — at least one test obtained at age <24 hours negative for SARS-CoV-2 with Negative serology (IgM or IgA) followed by positive RT-PCR at 24–48 hours or positive serology (IgM or IgA) at age 7–14 days that is corroborated by a positive serology test on a second sample obtained within 10 days of the first positive test.
(c) Postpartum transmission — at least one test obtained at age <48 hours was performed and negative for SARS-CoV-2 with Negative serology (IgM or IgA) at age <14 days followed by positive RT-PCR at age >48 hours OR positive serology (IgM or IgA) at age >14 days that is corroborated by a second positive serology test obtained within 10 days of the first positive test at age >14 days.