Received: 3 September 2021 | Accepted: 18 October 2021

DOI: 10.1002/ppul.25732

CASE REPORT

WILEY

Cavitary lung lesions in a neonate: Potential manifestation of COVID-19 related multisystem inflammatory syndrome

Anish Bakhle[1] | Kavita Sreekumar[1] | Bonny Baracho[1] | Sanjay Sardessai[2] | Maria Piedade Silveira[1]

[1]Department of Pediatrics, Goa Medical College, Bambolim, Goa, India

[2]Department of Radiodiagnosis, Goa Medical College, Bambolim, Goa, India

Correspondence
Kavita Sreekumar, Department of Pediatrics, Goa Medical College, Bambolim, Panaji, Goa, 403202, India.
Email: kantakum@yahoo.com

Abstract

Background: The hyperinflammatory state of multisystem inflammatory syndrome in children (MIS-C) predisposes to thromboembolic complications. We report a neonate with multiple cavitary lesions in lung, which we suspect could be a manifestation of multisystem inflammatory syndrome in neonate (MIS-N) following maternal COVID-19 infection during pregnancy.

Case Report: Eight-day-old neonate was referred with fever and fast breathing. Mother was positive for COVID-19 in 29th week. COVID-19 reverse-transcription polymerase chain reaction was negative, however, antibodies were positive. He had increased leucocyte count, and elevated levels of C-reactive protein (CRP), procalcitonin, ferritin, lactate dehydrogenase, and D-dimer along with bilateral reticulonodular opacities on chest radiograph and multiple nodules with evidence of cavitation in both lungs on chest tomography. All cultures were negative. A possible diagnosis of MIS was made. Infant was treated with intravenous immunoglobulin (IVIG) which he responded to with resolution of symptoms.

Conclusion: Neonates exposed to COVID-19 should be evaluated for thromboembolic complications and IVIG can be one of the treatment modalities.

KEYWORDS

COVID-19, multisystem inflammatory syndrome, neonate, pulmonary cavities, thromboembolism

1 | INTRODUCTION

In December of 2019, a new strain of Coronavirus emerged in Wuhan, China which resulted in the COVID-19 pandemic.[1] Among children infected by the virus, most are asymptomatic and only few, especially infants and those with co-morbid conditions, have severe disease.[2] However, multisystem inflammatory syndrome in children (MIS-C), is a more severe form of disease occurring 4–5 weeks after the infection, and capable of causing multiorgan failure.[3] The hyperinflammatory state of MIS-C predisposes to a prothrombotic coagulopathy making patients prone to thromboembolic complications including pulmonary thromboembolism (PTE).[4] Winant et al.[3] observed segmental pulmonary emboli in patients of MIS-C on thoracic imaging and recommended maintaining a high index of suspicion for embolism in these patients. There are now emerging reports of neonatal MIS (MIS-N), mainly presenting with cardiac manifestations, ground-glass opacities in the lungs and elevated inflammatory markers.[5–9] PTE is not common among the neonatal population and is a consequence of imbalance between procoagulant and anticoagulant systems.[10] Indwelling central lines, fluid instabilities, sepsis, liver dysfunction, congenital heart disease, occult malignancy, and systemic inflammation contribute to the risk profile for thromboembolism in critically ill neonates.[10,11] Here we report a case of a neonate born to a mother with COVID-19 infection during pregnancy, who presented to us with respiratory distress, elevated inflammatory markers, and having cavitary and nodular lesions in the lung, which we suspect could have resulted from thromboembolic complications of MIS-N.

1.1 | CASE REPORT

An 8-day-old male born at 37 weeks by Cesarean section to primigravida mother was referred to our unit with fever, lethargy, and respiratory distress. Mother was diagnosed with SARS- CoV2 infection at 29 weeks of gestation which was mild and had received antipyretics with home isolation. Maternal antibody levels were not done at the time. At delivery, she had tested negative for SARS-CoV2 and cord blood testing for the virus or antibody levels was not done. At admission, the total leukocyte count of the neonate was 31,200/cu. mm with 54% neutrophils, elevated CRP and procalcitonin, and bilateral reticulonodular opacities involving middle and upper zones of lungs on chest radiograph (Table 1, Figure 1A). The neonate was initiated on broad-spectrum antibiotics and oxygen via nasal canula. Real-time reverse-transcription polymerase chain reaction test for SARS-CoV2 was negative. Two blood cultures were sterile; cerebrospinal fluid and urine cultures were normal. The infant continued to have fever spikes along with respiratory distress and oxygen requirement. Given the maternal history of COVID infection, nonspecific radiographic findings, and sterile cultures, additional investigations were performed on Day 12 of life to investigate presence of inflammatory markers, COVID antibodies, D-dimer levels, echocardiogram, and high-resolution chest tomography (HRCT) (Table 1, Figure 1B,C). Qualitative antibody assay detected immunoglobulin G (IgG) antibodies against SARS-CoV-2 spike protein in neonatal serum, but no immunoglobulin M (IgM) antibodies. HRCT showed multiple nodules of varying sizes, grouped together at places in both lungs. Majority of the nodules showed evidence of cavitation. On follow-up scan, some nodules which were solid on the earlier scan showed evidence of cavitation. Imaging findings were suggestive of infectious thrombi in the lungs. Ultrasonography of the abdomen and contrast-enhanced CT of whole body were done. Multiorgan involvement with similar cavitary lesions or any malignant focus was ruled out. In view of the lab values suggestive of inflammatory syndrome (leucocytosis, elevated CRP and Procalcitonin, and reactive COVID-19 antibodies) with non-resolving symptoms, the decision was made to administer intravenous immunoglobulin (IVIG) at 1 g/kg/day for 3 days following which the child became asymptomatic and was off oxygen support. In view of the cavitary lesions, investigation for active Tuberculosis was carried out in the neonate and the parents which were also negative. To rule out the possibility of malignancy other tumor markers like β-human chorionic gonadotropin (HCG) and alpha-fetoprotein were done, which were within normal limits. Post IVIG, fever spikes subsided, distress gradually settled and neonate was discharged on breastfeeds. On follow-up at the age of 3 months, child is developmentally normal with adequate weight gain.

TABLE 1 Laboratory investigations in the neonate

Investigation	Reported values	Normal values
Hemoglobin	18.6 g/dl	11–19 g/dl
Total leucocyte count	31,200/cu.mm	6000–22,000/cu.mm
Neutrophil count	54%	40-75%
Platelet count	2,17,000/cu.mm	1,60,000–5,00,000/cu.mm
C-reactive protein	9.8 mg/L	0–6 mg/L
Serum procalcitonin	6.34 mg/L	0.1–4.2 mg/L
Serum ferritin	412 ng/ml	25–200 ng/ml
Serum LDH	412 U/L	290–775 U/L
Blood urea	17 mg/dl	6–25 mg/dl
Serum creatinine	0.45 mg/dl	0.2–1.1 mg/dl
D-Dimer	4894 ng/ml	<2700 ng/ml
SARS-CoV2 IgG antibody level[a]	12.8 COI	≤ 1 COI
Beta HCG[b]	<1.2 IU/L	< 10 IU/L
Alpha feto protein[b]	4058.4 ng/ml	1480–58,887 ng/ml

[a]Sienna™ COVID19 IgG/IgM Rapid Test Cassette qualitative detection by rapid chromatographic immunoassay; COI-cut off index

[b]Schneider DT, Calaminus G, Göbel U. Diagnostic value of alpha1-fetoprotein and beta-human chorionic gonadotropin in infancy and childhood. *Pediatr Hematol Oncol*. 2001;18(1):11–26.

2 | DISCUSSION

While vertical transmission of the SARS-CoV2 virus is rare due to low placental expression of the canonical receptors necessary for viral entry, placentas from infected mothers have shown thrombotic and vascular changes, which suggests that SARS-CoV2 is a highly procoagulant infection and even in the absence of fetal viral infection, it can trigger an inflammatory response, leading to multiorgan damage.[12,13] There are multiple case reports of neonates presenting with cardiac manifestations of shock, arrythmias, thrombosis, persistent pulmonary hypertension, as well as respiratory failure, neurological abnormalities, and hematological manifestations.[5–9,14] All these neonates had history of exposure to maternal COVID-19 infection during pregnancy, positive SARS-CoV2 antibodies, and elevated inflammatory and prothrombotic laboratory markers. In a case series of 20 neonates with MIS-N, reported by Pawar et al.,[5] they used diagnostic criteria modified from Centre of Disease Control criteria for MIS-C and interim guidance from American Academy of Pediatrics to accommodate lack of fever in neonates and source of primary infection (mother, instead of the child). The neonate described by us fulfilled these modified criteria. Coagulation abnormalities and thromboembolic phenomenon are listed as one of potential complications of MIS-C.[15] D-dimer levels have been recommended as the best test for evaluating hemostatic variations associated with COVID-19.[4] Such thromboembolic phenomena are also reported among infants. In a retrospective cohort study by Whitworth et al.,[15] out of 426 children aged 0–<21 years admitted with SARS-CoV2 infection or MIS-C, 20 patients were identified with thromboembolism with an incidence of 6.5% in MIS-C patients, out

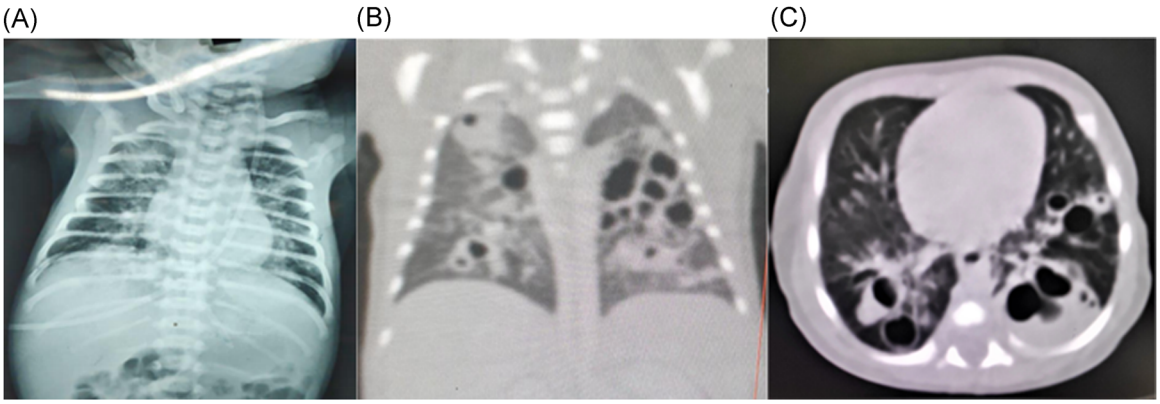

FIGURE 1 (A) Chest radiograph showing bilateral reticulonodular opacities in the middle and upper zones of the lungs. (B, C) HRCT coronal and axial view showing bilateral, multiple, nodular, and cavitary lesions in the lungs. HRCT, high-resolution chest tomography [Color figure can be viewed at wileyonlinelibrary.com]

of which three patients had pulmonary embolism. One patient was <1 year of age and had lower extremity deep vein thrombosis. Perveen et al.[16] reported a neonate born with an ischemic limb to a COVID-19 positive mother. Although, COVID antibodies were found in the newborn, the coagulation workup was normal. The thromboembolic event was thought to be a vascular effect of the COVID infection.[16] In another case reported by Engert et al.[7] a moderate preterm (33 5/7 weeks) infant had petechial bleeds, intracranial hemorrhage, and periventricular leukomalacia with elevated D-dimer levels and low platelet counts. The authors hypothesized this to be secondary to maternal hyperinflammatory response following SARS-CoV2 infection during second trimester of pregnancy.[7] In a case series of 20 neonates, Pawar et al. described one neonate with a cardiac thrombus.[5] Mamishi et al.[17] studied the CT findings in 24 children with SARS-CoV2 infection, age ranging from 3.5 to 9.5 years. Atypical findings were seen in 58% of the patients which included nodular and cavitary lesions. They suggested that atypical findings may be indicative of disease progression caused due to cytokine storm.[17] The HRCT in our case showed nodular lesions with central cavitation. In spite of an extensive investigative workup, we could not find a causal relationship of the CT scan findings to any of the conditions that could have caused it like bacterial or fungal sepsis, tuberculosis, congenital lung anomalies, or malignancy.[18] Endothelial injury by SARS-CoV2 and the hypercoagulability caused by the intense inflammatory response is capable of causing the PTE.[4,11] The presence of in-utero exposure to COVID 19 virus, elevated inflammatory markers and D-dimer levels lead us to conclude that our case could have had pulmonary thromboembolic phenomenon as a consequence of MIS-N which resulted in the rare CT picture of nodular and cavitary lung lesions. Maternal infection with SARS-CoV2 virus results in development of protective IgG antibodies which are transplacentally transferred to the fetus.[19] However, there can be autoantibodies generated against endothelial, gastrointestinal, and immune cells which result in immune dysregulation and hyperinflammation that can play a role in causing MIS-C.[20] Immunomodulatory therapies like IVIG and glucocorticoids, either alone or in combination, are shown to benefit and prevent progression of the disease by overriding the effect of autoantibodies and stimulate inhibitory Fc-receptors.[20] Due to possible long-term adverse neurodevelopmental effect of steroids, we decided to treat the neonate with IVIG alone. Also, due to lack of adequate evidence regarding its use in neonates with MIS-N, we did not give antithrombotic medications. The neonate responded to IVIG and had complete recovery of his clinical symptoms. Considering the potential possibility of the pulmonary lesions in our case to be secondary to MIS-N, we suggest that, clinical and laboratory evaluation to diagnose thromboembolic complications should be carried out in all symptomatic neonates exposed to SARS-CoV2 infection. Also, future research should be planned to study the use of antithrombotic prophylaxis in neonates exposed to the virus.

3 | CONCLUSION

MIS-N is no longer a hypothesis, but an actual disease entity with multiple reports available in literature. This disease is evolving with widening scope of symptomatology. Thromboembolic complications secondary to inflammatory response after SARS-CoV2 exposure should be considered in infants and children. It is essential for the neonatologists to consider the possibility of MIS-N in neonates with in-utero exposure for early diagnosis and management as well as share the data for better understanding of the disease and framing the best treatment practices. Diagnostic criteria and management strategies for MIS-N as well as thromboembolism in MIS-N should be developed, distinct from those currently available for children.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

ETHICS STATEMENT

Written informed consent was obtained from parents for publication of the details of their child's case.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

ORCID

Kavita Sreekumar http://orcid.org/0000-0002-7824-5839

REFERENCES

1. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med*. 2020;382(8):727-733.
2. Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 among children in China. *Pediatrics*. 2020;145(6):e20200702.
3. Winant AJ, Blumfield E, Liszewski MC, Kurian J, Foust AM, Lee EY. Thoracic imaging findings of multisystem inflammatory syndrome in children associated with COVID-19: what radiologists need to know now. *Radiol Cardiothorac Imaging*. 2020;2(4):e200346.
4. Carneiro JDA, Ramos GF, de Carvalho WB, Johnston C, Delgado AF. Proposed recommendations for antithrombotic prophylaxis for children and adolescents with severe infection and/or multisystem inflammatory syndrome caused by SARS-CoV-2. *Clinics (Sao Paulo)*. 2020;75:e2252.
5. Pawar R, Gavade V, Patil N, et al. Neonatal multisystem inflammatory syndrome (MIS-N) associated with prenatal maternal SARS-CoV-2: a case series. *Children*. 2021;8(7):572.
6. Kappanayil M, Balan S, Alawani S, et al. Multisystem inflammatory syndrome in a neonate, temporally associated with prenatal exposure to SARS-CoV-2: a case report. *Lancet Child Adolesc Heal Internet*. 2021;5(4):304-308. doi:10.1016/S2352-4642(21)00055-9
7. Engert V, Siauw C, Stock A, et al. Severe brain damage in a moderate preterm infant as complication of post-COVID-19 response during pregnancy. *Neonatology*. 2021;118:505-508.
8. McCarty KL, Tucker M, Lee G, Pandey V. Fetal inflammatory response syndrome associated with maternal SARS-CoV-2 infection. *Pediatrics*. 2021;147(4):e2020010132.
9. Khaund Borkotoky R, Banerjee Barua P, Paul SP, Heaton PA. COVID-19-related potential multisystem inflammatory syndrome in childhood in a neonate presenting as persistent pulmonary hypertension of the newborn. *Pediatr Infect Dis J*. 2021;40(4):E162-E164.
10. Paes BA, Nagel K, Sunak I, Rashish G, Chan AK. Neonatal and infant pulmonary thromboembolism: a literature review. *Blood Coagul Fibrinolysis*. 2012;23(7):653-662.
11. Haley KM. Neonatal venous thromboembolism. *Front Pediatr*. 2017;5(June):1-6.
12. Pique-Regi R, Romero R, Tarca AL, et al. Does the human placenta express the canonical cell entry mediators for SARS-COV-2? *eLife*. 2020;9:1-15.
13. Prochaska E, Jang M, Burd I. COVID-19 in pregnancy: placental and neonatal involvement. *Am J Reprod Immunol*. 2020;84(5):1-9.
14. Sankaran D, Nakra N, Cheema R, Blumberg D, Lakshminrusimha S. Perinatal SARS-CoV-2 infection and neonatal COVID-19: a 2021 update. *NeoReviews*. 2021;22(5):284–295. https://doi.org/10.1542/neo.22-5-e1001
15. Whitworth H, Sartain SE, Kumar R, et al. Rate of thrombosis in children and adolescents hospitalized with COVID-19 or MISC. *Blood*. 2021;138:190-198.
16. Perveen S, Millington KA, Acharya S, Garg A, Boyar V. Neonate born with ischemic limb to a COVID-19 positive mother: management and review of literature. *Case Reports Perinat Med*. 2021;10(1):-. https://doi.org/10.1515/crpm-2020-0086
17. Mamishi S, Heydari H, Aziz-Ahari A, et al. Novel coronavirus disease 2019 (COVID-19) outbreak in children in Iran: atypical CT manifestations and mortality risk of severe COVID-19 infection. *J Microbiol Immunol Infect*. 2021. 54(5):839–844. https://doi.org/10.1016/j.jmii.2020.07.019
18. Odev K, Guler I, Altinok T, Pekcan S, Batur A, Ozbiner H. Cystic and cavitary lung lesions in children: radiologic findings with pathologic correlation. *J Clin Imaging Sci*. 2013;3(1):60.
19. Flannery D, Gouma S, Dhudasia MB. Assessment of maternal and neonatal cord blood SARS-CoV-2 antibodies and placental transfer ratios. *JAMA Pediatr*. 2021;175(6):594-600.
20. Consiglio CR, Cotugno N, Sardh F, et al. The immunology of multisystem inflammatory syndrome in children with COVID-19. *Cell*. 2020;183(4):968-981. doi:10.1016/j.cell.2020.09.016

How to cite this article: Bakhle A, Sreekumar K, Baracho B, Sardessai S, Silveira MP. Cavitary lung lesions in a neonate: potential manifestation of COVID-19 related multisystem inflammatory syndrome. *Pediatric Pulmonology*. 2022;57:311-314. doi:10.1002/ppul.25732