Unveiling post-MIS-N cardiomyopathy by longitudinal multimodality global cardiac assessment from neonatal insult to 16-month follow-up

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ABSTRACT

A full-term male neonate presented on the 11th day of life with late-onset multisystem inflammatory syndrome-neonate (MIS-N) (cardioneurological compromise). Immediate anti-inflammatory modulation led to a gradual recovery of neurological and coronary lesions. However, temporal evaluation unmasked silent myocardial dysfunction in echocardiography validated further by elevated biomarkers, myocardial fibrosis in cardiac magnetic resonance imaging, and abnormal strain study persisting till 16 months of follow-up. This revealed a hitherto unknown and rare progression of MIS-N into dilated cardiomyopathy.

Keywords: Cardiac magnetic resonance imaging, dilated cardiomyopathy, multisystem inflammatory syndrome-neonate, strain imaging

INTRODUCTION

Post-COVID myocarditis both de novo as well as after mRNA vaccination has been increasingly reported in patients. Neonatal multi-inflammatory syndrome (MIS-N) was seen in clusters in India typically associated with a lag phase after adult waves. Initial isolated case reports were followed by case series from India.The usual pathophysiology postulated is hyperimmune fetal response secondary to transplacental transfer of SARS-CoV- IgG antibodies post occult/overt maternal antenatal infection. The long-term impact of neonatal hearts affected by MIS-N is rarely described. Here we are reporting a case of MIS-N unknown and rare progression into dilated cardiomyopathy.

CASE REPORT

A term (gestation age 37 + 3 weeks), apparently healthy male neonate was delivered by cesarean section to a primigravida mother after an uneventful antenatal period. The neonate had presented on the 11th day of life to a peripheral level III neonatal intensive care unit with poor feeding, lethargy, staring looks, and bluishness for the preceding 48 h. Suspecting neonatal sepsis, the neonate was admitted where two episodes of seizures with concomitant tachycardia and desaturation occurred. Intravenous phenobarbitone was administered as a first-line antiepileptic. Metabolic etiologies of neonatal seizures such as hypoglycemia and hypocalcemia were excluded. The neonatal tandem mass spectrometry report was normal. Intravenous antibiotics were started after sending a septic panel, including cerebrospinal fluid analysis which later came as negative. Neurosonogram demonstrated diffuse cerebral edema which persisted for 11 days.

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Cardiorespiratory system

Given the episodic desaturations (minimum SpO2 = 85%), and borderline mean arterial pressure (range: 32–35 mmHg), continuous positive airway pressure support was initiated along with dobutamine infusion at 10 μg/kg/min. The heart rate fluctuated from 140 to 190/min with frequent premature atrial ectopics [Figure 1].

Point-of-care echocardiography demonstrated a structurally normal heart, dilated left ventricle (LV), LV dysfunction with LV ejection fraction (LVEF) 40% on inotropic support (heart failure with reduced ejection fraction [HfrEF]), left anterior descending coronary artery aneurysm (*Z* score + 4.77), mild mitral and tricuspid regurgitation, normal pulmonary arterial pressures, left to right shunting foramen ovale, and trace pericardial effusion, but no intracradiac thrombi/regional wall motion abnormality.

This unusual multi-organ association involving neurological and cardiac (coronary aneurysm and myocardial dysfunction) was difficult to explain and prompted us to consider COVID-19-related MIS-N. Neonatal SARS-CoV-2 immunoglobulin (Ig) G antibody level was positive (more than 200 BAU/ml), and negative IgM and reverse transcription polymerase chain reaction suggested fetal COVID-19 exposure than neonatal COVID-19 infection. High COVID-19 IgG in neonates born to unvaccinated mothers against COVID-19 supports maternal COVID-19 infection during the antenatal period. Laboratory assays were done to assess the severity of immunological and end-organ damage. Marked elevation in D-dimer (7.03 ng/ml), serum ferritin (412 ng/ml), high-sensitive troponin I (hs Trop I) (38.9 ng/ml), serum lactate dehydrogenase (600 U/L), and N-terminal pro-brain natriuretic peptide (NT-proBNP) (70,000 pg/ml) favored the diagnosis of multisystem inflammatory syndrome-neonate (MIS-N). Although fever is a mandatory criterion for the diagnosis of multisystem inflammatory syndrome in children (MIS-C), its absence is almost the norm in MIS-N.

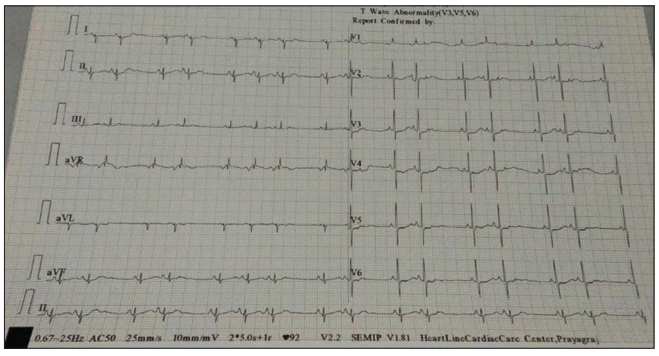

Figure 1: Twelve-lead electrocardiogram showing sinus rhythm with frequent atrial ectopics

Intravenous Ig (2 g/kg infusion) and steroids (IV methylprednisolone at 2 mg/kg/day) were started within 8 h of admission and continued for 5 days. Subsequently, tapering doses of oral prednisolone over 3 weeks were continued with frusemide and spironolactone for HFrEF management. Magnetic resonance imaging (MRI) brain revealed cerebral infarct with Wallerian degeneration. Aspirin was withheld as per the neurologist's opinion. The neonate clinically recovered and was discharged on the 24th day of life.

Serial follow-up pediatric data

The child progressively achieved normal milestones, growth, and development without residual neurological deficits. A follow-up brain MRI at 4 months showed a normal scan.

Serial follow-up cardiology evaluation

However, longitudinal echocardiographic examinations performed at 2 weeks, 1 month, 3, 6, 9, 12, and 16 months postdischarge revealed unanticipated trends. Normalization of coronary artery *Z* scores occurred within 6 weeks postdischarge. However, LVEF continued to trend within the 45%–48% range (Simpson's method) and dilated LV (*Z* score + 2.5). The basal ventricular septum displayed early adverse remodeling with ballooning and dyskinesia compared to adjacent segments. The NT-proBNP and hs Trop I levels were 856 pg/ml and 34.6 ng/ml at 6-month follow-up, respectively.

Cardiac MRI (cMRI) (3 Tesla) was done at 6 months of age under general anesthesia with breath-hold cine steady-state free-precession sequences. It showed subepicardial late gadolinium enhancement (LGE) on

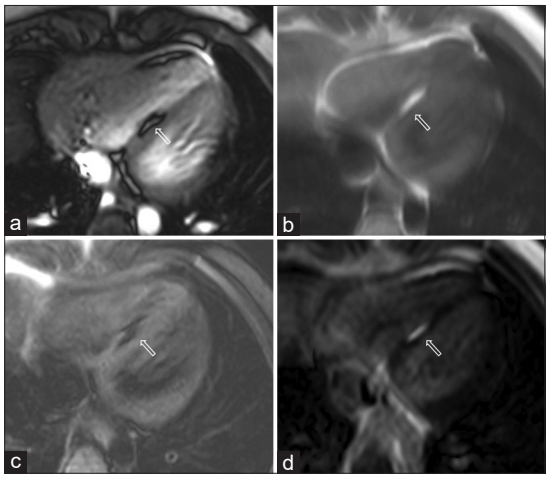

Figure 2: Four-chamber cine steady-state free-precession sequence (a) shows a hyperintense lesion in the inferior septum along the right ventricular side with peripheral blooming, the lesion is hyperintense on T1 (b)-weighted images, Suppression of signal on short tau inversion recovery sequence (c), The lesion shows delayed contrast enhancement on the phase-sensitive inversion recovery sequence (d)

the short axis, 2, 4, and 3-chamber views [Figure 2a-d]. Phase-sensitive inversion recovery sequences documented the involvement of basal inferior, mid-inferior, and lateral segments of the LV. The absence of myocardial edema ruled out acute myocarditis. Based on the distribution of the LGE pattern, myocardial ischemia was excluded as here it was not restricted to subendocardial location following a particular vascular territory pattern. This cMRI pattern reflected noncoronary, nonischemic etiology.

The cardioprotective medications were upgraded to carvedilol, spironolactone, and enalapril. His 16-month follow-up echo showed asymptomatic clinical status, normal sinus rhythm, and T-wave inversion in the lateral leads on the electrocardiogram. Standard echocardiography showed normalization of coronaries, ballooning of basal ventricular septum, and LVEF 45% by Simpson's method. The LV myocardial performance index was 0.61. On Tissue Doppler imaging (TDI), mitral medial S' velocity was 5.37 cm/sec, E'/A' ratio 1.5 while E/E' ratio was 12.2. LV myocardial performance index was 0.61 on TDI. An average of three cardiac cycles was taken to mitigate the lack of breath-holding. Sedated strain imaging at 16 months of age (i.e. 10 months post-cMRI) showed a borderline global longitudinal strain of −17.4% with localized, patchy segments of decreased strain rates: basal inferior septum −12.5, apical anterior lateral segment −10.1, and mid-anterior lateral segment −8.3 [Figure 3a and b].

DISCUSSION

Post-COVID-19 myocarditis both *de novo* and after mRNA vaccination has been increasingly reported in patients post-2020. Neonatal multi-inflammatory syndrome (MIS-N) was seen in clusters in India typically associated with a lag phase after adult waves. Initial isolated case reports were followed by case series from India.[1-6]

The usual pathophysiology postulated is hyperimmune fetal response secondary to transplacental transfer of SARS-CoV-IgG antibodies postoccult/overt maternal antenatal infection. It was grouped temporally into "early-onset" (within 72 h of delivery) and "late-onset" (beyond 72 h–28 days). MIS-N manifests heterogeneously with clinical mimicry with other neonatal illnesses. The scientific literature to date described a high preponderance of cardiac and coronary involvement in the acute phase.[1,4,5] The long-term impact of neonatal hearts affected by MIS-N is rarely described.

The salient aspects of the reported case are late-onset MIS-N presenting with cardioneurological involvement and the immediate immunomodulation with both intravenous Immunoglobulin and steroids leading to the gradual recovery of neurological and coronary aneurysms. However, asymptomatic silent myocardial dysfunction, adverse remodeling, elevated cardiac enzymes, and NT-proBNP, demonstration of myocardial fibrosis with HFrEF pattern in cMRI at 6 months of age, and abnormal strain imaging at 16 months were unfamiliar discoveries. This child represents that a unique subset of MIS-N may develop dilated cardiomyopathy (DCMP) in mid-long-term follow-up despite regular protocols. Clinical diagnosis of pediatric DCMP is often missed initially till gross heart failure develops. This case highlights two important take-home messages. Antenatal immune-mediated exposure to COVID-19 antibodies in the fetus may damage the developing myocardium irreversibly. The current echocardiography data post 16 months clinically extrapolate to the phase of chronic myocardial inflammation and fibrosis. The combination of cutting-edge cMRI, strain echocardiography, and biomarkers unmasked earlier the cryptic myocardial damage before the lag phase of clinical diagnosis. The moot question is how to identify this silent cohort. Whether we should adopt a uniform, regular evaluation in every post-MIS-N heart, including

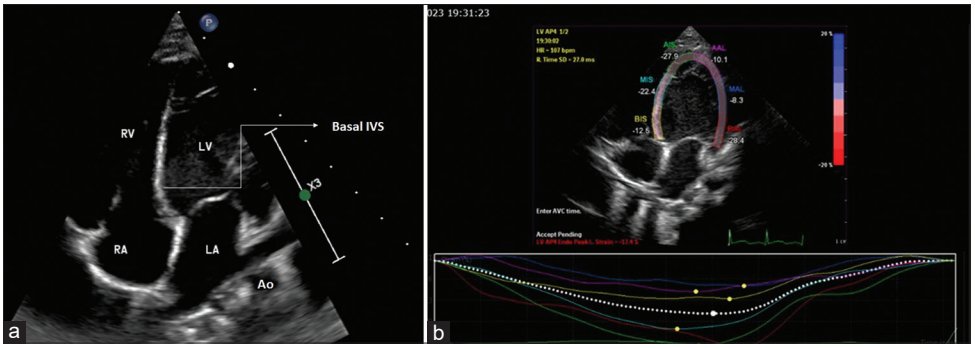

Figure 3: (a) Sixteen-month follow-up echocardiography. Apical four-chamber view showing increased echogenicity of the basal septum with ballooning (arrow), (b) Strain imaging shows borderline global longitudinal strain of −17.4% with localized focal segments of decreased strain rates: Basal inferior septum −12.5, apical anterior lateral segment −10.1, and mid-anterior lateral segment −8.3, IVS: Interventricular septum, LV: Left ventricle, RV: Right ventricle, RA: Right atrium, LA: Left atrium, Ao: Aorta

strain echocardiographic study, may be considered as reported by Minocha and Krishna.[7,8] Whether continuous administration of immune suppressants like steroids early anakinra or infliximab would have altered the natural history of chronic myocarditis is a point to ponder. The presence of fibrosis in cMRI is an independent predictor of cardiac events and sudden arrhythmogenic death.[9] The natural history, counseling of family, and therapeutic planning are modified with such evolving data.

MIS-C was initially reported in April 2020 from the USA and as pediatric inflammatory multisystem syndrome-TS from the United Kingdom and Ireland from the British pediatric surveillance unit. This was a new disease developing in 1% of affected children with COVID-19, initially after a lag phase of 2–6 weeks postinitial infection but with almost 10 times higher rates of hospitalization and mortality than other pediatric COVID-19 cases.[10,11]

MIS-N is a distinctive subgroup of MIS-N where transplacental transfer of maternal antibodies triggers unusual responses within *in situ* fetuses and neonates. This immune-mediated myocarditis may not always be transient. The reported case symbolizes that identical sequential myocardial damage as in viral myocarditis like acute, subacute, and chronic phases leading to DCMP is also probable. The first two stages are very challenging to diagnose in the unborn fetus. The difference in age groups where MIS-C involves predominantly older children and adolescents whereas MIS-N affects fragile neonates needs to be remembered. MIS-C with its tell-tale signs is diagnosed earlier and more easily than MIS-N. There are scanty data on long-term cardiac outcomes in MIS-C as followed up by cMRI. About 15%–29% of MIS-C was reported in late cMRI studies to develop various chronic sequelae, including pericardial effusion, aneurysms, and cardiac dysfunction.[12] Long-term cardiac assessment of MIS-N both globally and specifically from India is sparse, and probably, our case is a harbinger of the rare consequences. The 2nd and 3rd waves of the COVID-19 pandemic in India were so overwhelming that research was focused on the sickest. Probably, it is time to take a long-term 360° view and create a multicentric database analysis to answer these riddles.

CONCLUSION

This case alerts us about the need for long-term cardiac surveillance in post-COVID-19 MIS-N. Awareness creation in pediatric and cardiology communities is our best weapon in low middle income countries (LMIC) setups. As echocardiography and biomarkers have become widely available post-COVID-19, they may be considered as first-line steps and if abnormal, should be validated with strain imaging and cMRI in advanced institutes. A multidepartmental holistic evaluation of each MIS-N neonate combined with serial data collection and analysis would help to assort such odd ones. However, given the adverse long-term prognosis of this rare neonatal cohort, focused research is the need of the hour.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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