Case Report

Six-month outcome of multisystem inflammatory syndrome with persistent neutropenia in neonate: A case report and review of literature

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Abstract

Multisystem inflammatory syndrome in Children (MIS-C) is a postinfectious immune mediated complications seen in children and develop after 4-6 weeks of severe acute respiratory syndrome coronavirus -2 (SARS-CoV-2) infection, however, it is rare in neonates. The index case was admitted at day 19 of life with complaints of fever, loose stools and rash. Baby was discharged after 1 weeks with diagnosis of Multisystem inflammatory syndrome with persistent neutropenia. We follow up the case at 6 weeks, 12 weeks and 6 months of life. Growth, neurodevelopment and hematological parameters were monitored over time. We are reporting this follow up of MIS-N with persistent neutropenia because it is very rare, organ specific manifestations, effect on growth & development is unknown and needs to be reported. Improvement in hematological parameters and markers of coagulopathy & systemic inflammation required months before they return to baseline. There are no long-term sequelae on growth and neurodevelopment.

Keywords: Follow-up, multisystem inflammatory syndrome in children, neonate, neutropenia, SARS-CoV-2

Introduction

As of date March 20, 2022, coronavirus disease 2019 pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected more than 46 crore people worldwide and leads to more than 60 lakh deaths all over the world.[1] Multisystem inflammatory syndrome postulated to be a hyperinflammatory immune complication post SARS-CoV-2 virus infection.[2] Fever, respiratory distress and gastrointestinal disturbances are the common short-term outcomes of COVID-19 infection in neonates.[3] Fever, rash, shock, feed intolerance, pericardial effusion, ascites, abnormal electrocardiogram, seizures, renal failure, neutropenia, etc., are the presenting features of MIS-C in neonates (MIS-N).[4-7] Davies P *et al.* showed that echocardiography parameters and hematological parameters were not normalized in children recovered from MIS-C even after 1 year.[8] Contrary to follow up reports in children, medium- and long-term outcomes and sequelae of COVID infection in neonates are unreported. We report 6-month follow-up of multisystem inflammatory syndrome in a neonate (MIS-N).

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Case Presentation

Baby was admitted on day 19 of life with complaints of fever with multiple episodes of loose stools. Rest of the clinical

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examination was normal at time of admission. Baby delivered by caesarean section at 39 weeks of gestational age. Mother had an episode of cough and cold one week before delivery. Coronavirus real-Time polymerase chain reaction (RT-PCR) was negative for the neonate and positive for the mother at time of admission. Work-up for late onset neonatal sepsis screen came negative, but C-reactive protein was raised. Blood culture, urine culture and cerebrospinal fluid culture were sterile. Baby remained febrile despite intravenous antibiotics and round the clock antipyretics and developed rash on day 2 of admission. Echocardiography showed structurally normal heart with preserved ejection fraction. Complete blood count (CBC) shows total leukocyte count within normal limit but falling trend of absolute neutrophil count (ANC) [Table 1]. Persistent fever without a focus with high CRP, multiorgan involvement (skin and gastrointestinal tract) and deranged levels of markers of coagulopathy raised the suspicion of MIS-N and work-up for the same came positive as per definition given by World Health Organization.[2]

Treatment

On 3rd day of admission, intravenous immunoglobulin (IVIg) and aspirin were started in antiplatelet dose. Baby showed clinical response and fever subsided within 24 hours of immunomodulatory therapy. After admission, antibiotics were stopped on 5th day.

Outcome and follow-up

Baby remained hemodynamically stable throughout his stay and discharged from hospital on breast feeds, multivitamin drops and aspirin with advice for regular follow-up in high-risk clinic. Neutrophil count, systemic markers of inflammation and coagulopathy took months to reach baseline values [Figure 1]. 2D-ECHO showed normal systolic and diastolic functions with normal coronary arteries over the time. Anthropometric parameters were calculated at time of discharge, at 6 weeks, at 12 weeks and 6 months of age, and Z scores were calculated [Figure 2]. Developmental Assessment Scale for Indian Infants (DASII) was used for the assessment of neurodevelopment at 12 weeks and 6 months of age showed normal development without even minor deviation in neurodevelopment.[9,10]

Discussion

Diagnosis of multisystem inflammatory syndrome in children requires fever ≥3 consecutive days, multiorgan involvement (shock, mucocutaneous, gastrointestinal and neurological), laboratory evidence of inflammation (↑C-reactive protein, erythrocyte sedimentation rate, ferritin, procalcitonin), ≥2 features of disease activity (neutrophilia, lymphopenia, thrombocytopenia, echocardiography confirmed cardiac involvement, myocarditis, evidence of coagulopathy) and evidence of recent COVID-19 infection or exposure in the absence of any other possible explanation for inflammation.[2] MIS-C affects children around 10 years of age, approximately 4-6 weeks after initial COVID-19 exposure.[11,12] Pathophysiology of MIS-C is still under evaluation, and an aberrant cellular and humoral response hypothesized to be responsible for this hyperinflammatory immune response post-SARS-CoV-2 infection in children.[13,14]

In a retrospective cohort study, Penner J *et al.* reported that cardiac, gastro-intestinal, hematological, renal abnormalities and

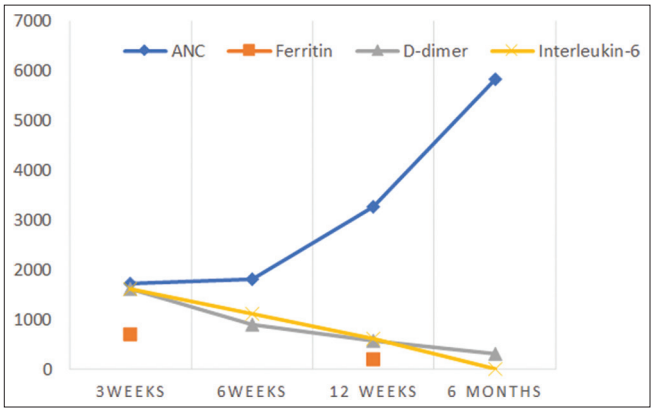

Figure 1: Absolute neutrophil count (ANC) & Inflammatory markers of neonate

Table 1: Laboratory parameters of the neonate

Laboratory parameters	03/06/21	12/06/21	12/09/21	15/12/21
Hb (gm/dl)	15.5	14.0	13.2	12.6
TLC (per cmm)	11800	11200	8600	10600
Neutrophils (%)	65	14	38	55
Lymphocytes (%)	32	70	40	39
Platelet Count (Per cmm)	97000	524000	443000	429000
Blood, Urine and CSF Culture	Sterile			
Urine routine/micro	Normal			
CSF- cells	7 (100% Lymphocytes)			
Protein (mg/dl)/Sugar (mg/dl)	55.9/40			
SARS-CoV-2 IgG antibody (reactive ≥1.0 S/Co, signal to cut off ratio, SARS-CoV-2 IgG)	1.47			
Ferritin (reference range 25–300 ng/ml)	710.30		210	
D-dimer (reference range 0–500 ng/ml)	1620	898	570	315
Interleukin-6 (Ref value 0.5–6.4 pg/ml)	1624	1115	614	15

CSF: Cerebrospinal fluid, SGOT: Serum glutamic-oxaloacetic transaminase, SGPT: Serum glutamic-pyruvic transaminase, TLC: Total leukocyte count

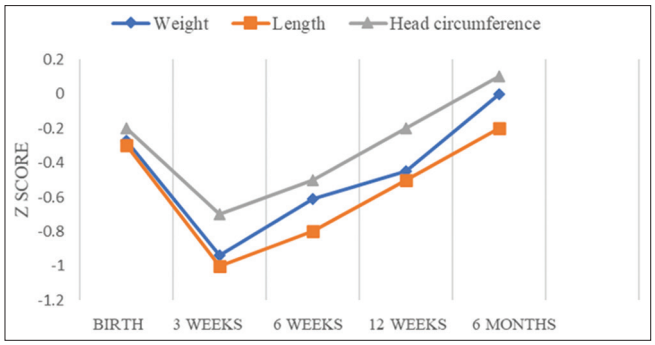

Figure 2: Growth of the index case over 6 months

raised marker of systemic inflammation in MIS-C resolved on follow-up with minor deviation in neurological examination.[15] Growth and neurodevelopment remain normal in the index case over the time. Normal systolic function, recovery of coronary artery dilatations/aneurysms with continuance of diastolic functional abnormalities was shown in children recovered from MIS-C on long-term follow-up in a tertiary care center in New York.[16] In our case, serial echocardiography shows normal ventricular functions and normal coronary dimensions on follow-up. Our case did not develop any clinical finding suggestive of bleeding or thrombotic complication.

A higher neutrophil-to-lymphocyte ratio with thrombocytopenia is more pronounced in multisystem inflammatory syndrome in children.[14] Davies P *et al.* reported one year outcome in children post-multisystem inflammatory syndrome and showed raised markers of inflammation in 10–17% of patients, persistent abnormalities in markers of coagulopathy in 25% of children with 2% of them having persistent neutropenia at end of one year.[8] Zuccotti *et al.* suggest that there are no long-term impact of MIS-C on children health.[17] In index case, neutropenia lasted for weeks and resolved spontaneously on follow-up. Serum ferritin, D-dimer and interleukin-6 gradually returned to baseline over the months. There are few case reports showing neutropenia complicating MIS-C in infants and requiring pharmacologic treatments.[18,19] Differential expression of ACE-2 (angiotensin-converting enzyme-2) receptor, differential immune response to virus or cross-reactive antibodies due to repeated upper respiratory tract infections are the postulated mechanism for variable response to COVID-19 infection in children.[20-22] Pathophysiology behind hematologic-immune dysregulation in MIS-C in infants is still not clear, it is different as compared to older children and adults, and elaborative studies are required to explicate natural course in infants with multisystem inflammatory syndrome post-COVID-19 infection.

Conclusions

In summary, we report 6-month follow-up of MIS-N with persistent neutropenia. Improvement in hematological parameters and markers of coagulopathy and systemic inflammation required months before they return to baseline. There are no long-term sequelae on growth and neurodevelopment. Short- and medium-term outcomes of multisystem inflammatory syndrome in neonate seem to be promising. Adequately powered studies will help in confirmations of our findings and delineate the natural course of MIS-N.

Key Points

- Multisystem inflammatory syndrome in children (MIS-C) is rare in neonates.
- Improvement in deranged hematological parameters took months.
- Anthropometric parameters (weight, head circumference and length) remain unaffected.
- There are no long-term sequelae on growth and neurodevelopment.

Declaration of patient consent

Consent from parents was taken.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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