Case Series

Non-COVID infections causing MIS-C in COVID recovered children: An association or co-illness – A case series

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Abstract

With the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, multi-system inflammatory syndrome (MIS-C) is being reported all across the world. Why some children develop it whereas others do not and the various implicating agents for the same are not clear. It has been seen that various infections are associated with immune mediated diseases. Whether new infections, in COVID recovered children, can lead to the cascade of MIS-C is still a matter of debate. We report a case series of four cases of MIS-C all subsequent after bacterial or viral infection in COVID recovered children. All children had a documented evidence of past SARS-CoV-2 infection and present bacterial or viral infection. They were given the required management as per the concerned infection but none improved after standard therapy. All children showed drastic improvement after initiation of specific therapy for MIS-C. It is important to understand increased risk of MIS-C with new onset viral and bacterial infections in COVID recovered children.

Keywords: COVID, infections, inflammatory, MIS-C, shock

Introduction

Since the beginning of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, an increasing number of countries reported cases of a systemic hyperinflammatory condition defined as multi-system inflammatory syndrome in children (MIS-C). Why some children develop MIS-C whereas others do not is still not clear. Whether there are any genetic causes or acquired causes for the same needs to be studied further. As it is a severe life-threatening condition, it becomes a matter of utmost priority for the primary care and family physicians to find out the implicating agents, for prevention and early treatment.

We report a case series of four cases of MIS-C all subsequent after a bacterial or viral infection in COVID recovered children.

Case 1

A $4^{1/2}$-year-old female child, presented with high grade fever and right upper abdomen pain for eight days. It was associated with gradually progressive, generalized abdominal distension, vomiting, and one episode of altered blood in stools. There was no history of cough, breathing difficulty, headache, neck stiffness, or loose stools. On examination, she was conscious but lethargic. Vitals showed tachycardia with regular feeble pulses, tachypnea and hypotension. Child had

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normal anthropometry. On general examination she was pale, icteric, bilateral pedal edema and SpO2 of 90% on room air. Per abdominal examination showed hepatomegaly (Liver span 12 cm) with shifting dullness. Respiratory examination revealed bilateral decreased air entry in infra-scapular and basal region. Other system examination was normal. Airway, breathing, and circulation were restored with help of intravenous fluids and oxygen. Intravenous antibiotics were started. Blood investigations suggested anemia, thrombocytopenia, raised liver enzymes, and high c reactive protein (CRP) [Table 1]. As Dengue NS1 was found to be positive, patient was treated as severe dengue and managed according to the standard guidelines. In next 48 hour of admission, respiratory distress improved and patient was gradually weaned off from oxygen. Although the blood parameters in the hemogram improved, child continued with high grade fever and persistent jaundice. Blood and urine cultures showed no growth. Meanwhile, COVID antibody sent in view of raised CRP turned out to be positive. Subsequently, Ferritin and D-Dimer were also high [Table 1]. The diagnosis was revised as severe dengue with MIS-C (post-COVID) and child was started on intravenous methyl prednisolone (IVIG not given due to financial constraints) and enoxaparin. After initiation of Methyl prednisolone significant improvement was noted in next two to three days. Fever subsided and inflammatory markers declined. Echocardiography done was normal. Based on the clinical picture and investigations, we made a final diagnosis of severe dengue with MIS-C.

Case 2

A 5-year-old female child, presented with high grade fever and vomiting for two weeks and generalized abdominal distension for five days. There was no history of cough, breathing difficulty, headache or loose stools. On admission, she was febrile, heart rate was 110 beats/min (regular, good volume pulses), respiratory rate 28/min and blood pressure of 90/62 mmHg. Her anthropometry was normal for age. On general examination child appeared severely pale. Abdominal examination showed hepatosplenomegaly with no ascites. Other system examinations were normal.

In view of acute febrile illness intravenous antibiotics (cefotaxime) and IV fluids were given. On investigation, hemoglobin was 3.6 mg/dl, for which packed cell transfusion was given. Other reports showed leucopenia, raised CRP, and transaminitis [Table 1]. Blood culture was positive for salmonella typhi, sensitive to Ceftriaxone and Azithromycin. As the child did not show any clinical improvement over next four days, oral azithromycin was added. Despite the above measures, fever persisted and CRP remained to be high. A clinical suspicion of MIS-C was considered. COVID antibodies, D-dimer and ferritin were found elevated. Parents were counselled on the need for IVIG but due to unaffordability, treatment with Methyl prednisolone, and enoxaparin was started. 2D-Echocardiography done was normal. Following the initiation of Methyl prednisolone, we found significant improvement over next three to four days. Fever spikes gradually subsided. Based on the clinical presentation and investigations, the patient was diagnosed as a case of enteric fever with MIS-C.

Case 3

A 9-year-old female child, presented with two days history of high-grade fever, vomiting and one episode of tonic clonic seizures lasting for 1-2 min followed by loss of consciousness for 10-15 min. There was no history of cough, headache, rash, pain abdomen, decreased movement of any limb or altered behavior or previous seizures. On admission, child was drowsy (Glasgow Coma Scale score 10/15). Her heart rate was 130/min, regular low volume pulses, respiratory rate 26/min and blood pressure recorded as 80/50 mmHg. She was febrile with saturation of 92% on room air. Her anthropometry was normal for age. On general examination child appeared pale with no visible neurocutaneous markers. On CNS examination, meningeal signs

Table 1: Laboratory reports of the cases during the hospital stay

Day of admission	Hb g/dl	TLC/ mm^3	Platelets/ ul	HCT (%)	AST IU/L	ALT IU/L	CRP mg/L	D-Dimer ng/ml	Ferritin ng/ml	Widal O, H >1:160	Dengue NS 1/IgM ab	Blood culture	SARS-COVID antibody
Case 1													
Day 1-2	7.3	3800	60,000	24	216	242	110	4455	229	Negative	Positive		
Day 5-7	8.8	7500	1,50,000	27.6	157	102	85	810	130			Sterile	Positive
Day 12-14	12.4	10000	4,50,000	39	47	40	60	473	40				
Case 2													
Day 1-2	3.4	5100	2,25,000	11.2	150	98	187	4000	1354	Positive	Negative		
Day 5-7	7.4	7700	2,53,000	22.2	88	60	80	1800	653			Salmonella typhii	Positive
Day 12-14	10	12800	3,00,000	35.1	40	37	40.7	233	35.4				
Case 3													
Day 1	5.2	4000	1,20,000	24.6	174	130	135	6790	214	Negative	Negative		
Day 5-7	8.0	8500	1,60,000	28.7	92	68	98	2480	133			Staphylococcus aureus	Positive
Day 12-14	11	12000	2,25,000	30	48	40	68	1500	62.9				
Case 4													
Day 1-2	11.8	2400	3,00,000	52	44	68	145	10,800	252	Negative	Negative	Staphylococcus (Previous)	Positive

Abbreviations: Hb: hemoglobin, TLC: total leukocyte count, HCT: hematocrit, AST: aspartate transferase, ALT: aminotransferase, CRP: C-reactive protein

were positive. Pupils were bilateral normal size and reacting to light. Tone was increased in all 4 limbs and deep tendon reflexes were exaggerated. There was no focal neurological or cranial nerve deficit. Other systemic examinations were normal. Patient was admitted in pediatric intensive care unit and managed as a case of acute encephalitis. She was started on intravenous fluid and subsequently on ionotropes, antiepileptics, broad spectrum antibiotics, antiviral, and antimalarial empirically. Contrast-enhanced computed tomography of the abdomen (CECT) brain suggested right hemimegaloencephaly with lacunar infarct. Over next 4-6 hours of admission, child deteriorated with falling GCS (<8/15) following which she was put on mechanical ventilation. Blood investigations showed severe anemia [Table 1] for which packed cell transfusion was given. Meanwhile, blood culture grew Methicillin-resistant *staphylococcus aureus* sensitive to Meropenem following which antibiotics were upgraded. Despite upgradation of antibiotics, patient's condition did not improve over next 48 hours. In view of persistent fever and elevated CRP, COVID antibody, D-dimer, and ferritin were sent and found positive [Table 1]. Methyl prednisolone and enoxaparin were added to patient's treatment regimen. Intravenous immunoglobulin though being first line for MIS-C could not be given due to poor affordability. Echocardiography report was normal. Child showed a marked improvement over next 48-72 hours along with improvement in laboratory parameters. Inotropes were tapered and child gradually weaned off from ventilatory support in next two days. She was discharged at completion of antibiotics with regular follow up. A final diagnosis of MIS-C with Meningoencephalitis was kept.

Case 4

A 4-year-old female child was brought in emergency department with active seizure in form of right sided tonic clonic movements of upper and lower limb, since last 30 to 45 min. There was no history of cough, vomiting, headache, pain in abdomen, decreased movement of any limb, or altered behavior. Patient was admitted one month back to a tertiary care hospital with left hand abscess and high grade fever, further associated with splenic abscess and pericardial effusion secondary to staphylococcal aureus infection found on blood culture. She received meropenem, vancomycin, and clindamycin along with primary work up for immunodeficiency. The patient was discharged on oral antibiotics five days prior to the present episode. During her stay at home, she was asymptomatic. On admission to our hospital, she was febrile with heart rate of 130/min (normal volume regular pulses), RR 34/min and blood pressure 100/60 mmHg. She was drowsy (GCS 10/15) and SpO2 of 97% on room air. Pupils were bilaterally reacting to light. Neurological examination showed exaggerated deep tendon reflexes with no focal deficits or meningeal signs. Rest of systemic examination did not reveal any abnormality. Antiepileptics Phenytoin and Levetiracetam along with other supportive treatment were given. With a suspicion of brain abscess, higher antibiotics were added as per the previous culture sensitivity report. Investigation showed leukocytosis along with raised CRP [Table 1]. MRI brain revealed small homogenously enhancing lesion in left cerebral hemisphere and right thalamus with edema in left frontal region. In view of high CRP and our past experience of infection leading to MIS-C, we got D-Dimer, Serum Ferritin and COVID antibody levels done, which turned out to be highly elevated. Hence a diagnosis of MIS-C secondary to disseminated staphylococcus sepsis was kept. The patient was advised for IVIG and enoxaparin however patient was referred back to the initial government center due to financial constraints. We wish to highlight this case as it had a presentation similar to our abovementioned cases.

None of the above mentioned four patients had a known history of COVID infection in the past or previous report positive for SARS-CoV-2 virus.

Discussion

A lot of infections have been well defined in literature to be associated with immune mediated diseases such as HLH, Kawasaki, and lymphoproliferative disorders.[1-3] Kawasaki-like disease has already been described in COVID recovered children suggesting immune dysregulation in these children.[4] Studies have shown persistence of immune dysregulation, after COVID infection, for six months or more.[5]

Any infection, such as SARS-CoV-2 results in extensive antigen-antibody reaction. Those complexes which do not get cleared develop type 3 hypersensitivity reactions leading to multisystem inflammatory syndrome. All four cases in our center had features of MIS-C along with an associated bacterial or viral infection. The definition of MIS-C related to COVID-19 states exclusion of microbial causes of inflammation as one of the criteria for diagnosis.[6] Hence, to state that the inflammatory conditions in these children is due to past COVID-19 infections (as evident by positive antibody response) or is due to immediately preceding bacterial/viral infection is difficult to be commented upon. It is also possible that in the setting of an already existing immune dysregulation (post-COVID), new infection in some such predisposed children cause an exaggerated immune response leading to MIS-C. This hypothesis can be explained by recent article published by Murray *et al.* in 2020. It states that bacterial components of streptococcus and staphylococcus carry molecular components sharing homology to super antigens. Super antigens induce Interleukin-1 leading to polyclonal activation of Tcell, B cell, and complement system causing severe inflammatory response. SARS-CoV-2 also possesses superantigen like qualities similar to staphyloccus endotoxin. This molecular mimicry may be one of the reasons for an exaggerated immune response in our cases.[7-10]

Categorically we also noted delayed presentation of MIS-C in all four cases. The most defined time period for developing MIS-C after COVID has been found to be four to eight weeks as per the available literature till date.[11] But all four patients in our series presented after 12 weeks, assuming their exposure in peak COVID wave during April-May 2021. As we do not have a definite history

of COVID exposure in any of the four patients we expect that their exposure must have happened during peak COVID surge. Delayed presentation of MIS-C in these cases can be explained in the light of the recent study showing prolonged immune dysregulation after SARS-CoV-2 infection lasting six months or more.[12,13] As stated previously, fresh infections may act as triggers to initiate the cascade of MIS-C in such children rather than only past SARS-CoV-2. As the studies are meager to understand why some children develop MIS-C whereas other do not, we have postulated a list of possible causes which needs further research:

1. Prolonged dysregulation of immune system, especially complement system after SARS-CoV-2 infections
2. New viral/bacterial infection leading to a cascade of immune reactions in covid recovered children with existing immune dysregulation
3. Genetic variants and molecular mimicry between SARS-CoV-2 and other bacterial or viral subunits leading to exaggerated immune response.

More studies are required to understand the pathophysiology and risk factors behind this condition. Moreover, a lot of primary care and family physicians are the first point of contact for pediatric and adolescent patients. MIS-C often gets missed in the initial stages due to non-specific sign and symptoms. Delayed diagnosis can lead to unwanted complications and poor outcomes. Hence, it becomes essential for all primary care physicians to be aware of this condition and timely intervention.

Take home messages

1. MIS-C is an emerging life-threatening condition in COVID recovered children.
2. Intravenous immunoglobulin and steroids are the mainstay of treatment.
3. Timely recognition by the primary care physician can help in improving the outcomes.

Author contribution

NB, PA and R. finalized the draft and performed the literature review. SS and NG prepared the initial draft and managed the patients. JK, NB, R. managed the cases and did the critical evaluation. All authors read and approved the final manuscript.

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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Conflicts of interest

There are no conflicts of interest.

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