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Case Series

Multisystem inflammatory syndrome in children associated with 2019 novel coronavirus (SARS-CoV-2) infection

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ABSTRACT

Being in the middle of a global pandemic of coronavirus disease (COVID-19), caused by the novel coronavirus SARS-CoV-2 there were never ending speculation regarding the occurrence, causation, spread and treatment of the disease which warranted a never ending research on this aspect. Initially was thought to be affecting children with lesser severity, but now it has been observed that, SARS-CoV-2 infection has recently been associated with a novel set of clinical manifestations presently called multisystem inflammatory syndrome in children (MIS-C) which was recognised at the outset by the United States, which lacked published reports by then. Here, we describe three critically ill patients with the spectrum of MIS-C associated with SARS CoV- 2 infection presenting to a tertiary-care center in India. Clinical presentation of MIS-C with multi-organ involvement and elevated inflammatory markers may have a presentation which is similar to the presentation as seen in Kawasaki disease and toxic shock syndrome. But now it has been presently understood to be a separate phenomenon and it has been related to a post-viral immune-mediated inflammatory process, and the pathogenesis of the occurrence of this syndrome complex still remains unclear.

Keywords: Multisystem inflammatory syndrome in children, SARS CoV- 2, COVID-19

INTRODUCTION

Being in the middle of a global pandemic of coronavirus disease (COVID-19), caused by the novel coronavirus severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) there were never ending speculation regarding the occurrence, causation, spread and treatment of the disease which warranted a never ending research on this aspect. Initially was thought to be affecting children with lesser severity, but now it has been observed that, SARS-CoV-2 infection has recently been associated with a novel set of clinical manifestations presently called multisystem inflammatory syndrome in children (MIS-C) which was recognised at the outset by the United States, which lacked published reports by then.[1-4] Here, we describe three critically ill patients with the spectrum of MIS-C associated with SARS CoV-2 infection presenting to a tertiary-care center in India.

CASE SERIES

Case 1

A 8 year old female child who was febrile and in respiratory failure and there showed no other significant past medical history, presented to the EMR with alerted mental status, diarrhoea, vomiting, conjunctivitis, shortness of breath, and facial swelling. The child was admitted to the pediatric intensive care unit (PICU) and intubated for hypoxic respiratory failure. An echocardiogram showed borderline low systolic function with a shortening fraction of 30–32%. She was treated with dopamine and milrinone and required respiratory support with bilevel positive airway pressure (BiPAP). Routine

blood investigations showed leukocytosis, neutrophilia, and hypoalbuminemia, with elevated levels of troponin and BNP (Table 1). The parameters observed in cerebrospinal fluid (CSF) finding examination were consistent with the parameters of aseptic meningitis (white cell-count of 100/µl with 56% lymphocytes, 34% monocytes, a normal glucose of 86 mg/dl (normal range 50 to 75 mg/dl), and protein of 38 mg/dl (normal range 15–45 mg/dl). The patient had a negative respiratory viral panel (RVP) and a positive SARS CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR). Further stay at hospital course was complicated by ever deteriorating kidney function manifested by high serum creatinine. The patient was treated with broad spectrum intravenous antibiotics like ceftriaxone and linezolid as well as hydroxychloroquine, methylprednisolone, and enoxaparin. On progression of events, the child became afebrile on day 3 of hospitalization. Blood, CSF, and urine cultures were negative. Testing for Lyme, *Mycoplasma pneumoniae*, cytomegalovirus (CMV), West Nile virus, and Epstein Barr virus (EBV) were all negative. Testing for other bacterial, viral and fungal organisms which are done as a standard protocol in the local area are found to be negative.

Case 2

A 7 year old male child with no significant past medical history presented to our set up, after having two days of febrile illness he had associated symptoms like progressively worsening diffuse abdominal pain and multiple episodes (4-5 times per day) of profuse watery, non-bloody, non-mucoid stools. Few hours before arriving to the hospital, he developed pink eyes and became lethargic which alarmed the parents to approach to our facility. In the emergency department the child was not found to have any chest pain, shortness of breath, or vomiting. The vitals were observed to be have a temperature of 103°F, heart rate of 140 beats per minute. Oxygen saturation and blood pressure were normal. Physical examination showed a remarkable conjunctival injection, a generalized blanching rash, and diffuse abdominal tenderness. But, roughly 2.5 hours after admission, she became hypotensive (blood pressure of 80/40 mmHg) needing multiple fluid boluses and inotropic support with norepinephrine. Blood and urine samples were obtained and sent for culture sensitivity which was found to be negative, but blood examination showed to have neutrophilia, lymphopenia, hypoalbuminemia, elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), fibrinogen, D-dimers, ferritin, troponin, and B-type natriuretic peptide (BNP). Clinical characteristics and laboratory evaluation are summarized in Table 1. In addition to that, the patient had a negative respiratory viral panel (RVP). SARS-CoV-2 RT-PCR was positive. The patient was under intravenous antibiotic cover with drugs like ceftriaxone and linezolid for 2 days until blood, urine, and stool cultures were negative. Imaging studies did not show any significant and remarkable changes (Table 1). He was given intravenous immunoglobulin (IVIG) at 2 g/kg, steroids, and enoxaparin for treatment and was discharged home after a week of hospital stay.

Case 3

A 10 year old girl with no significant past medical history presented to the EMR with afebrile, which was complained to be present since the past four days with associated headaches, vomiting, abdominal pain, diarrhea, conjunctivitis, and rash. She had a positive history of exposure to grandfather who was positive for COVID-19 two weeks earlier. Upon vital examination at ER, she was showed to have a temperature of 103ºF, heart rate of 138 beats per minute, respiratory rate of 24 breaths per minute, and oxygen saturation was 100% on room air. Two hours later, she got hypotensive with blood pressure of 70/40 mmHg requiring pressor support and developed severe distress which needed intubation and mechanical ventilation. CBP shown to have lymphopenia, thrombocytopenia, hypoalbuminemia, elevated levels of inflammatory markers, D-dimers, ferritin, troponin, and BNP as shown in Table 1. The patient has had a negative respiratory viral panel (RVP) and SARS-CoV-2 PCR. Antibody testing for SARS-CoV-2 (SARS-CoV-2 IgG) was positive.

The patient was given broad spectrum intravenous antibiotics like meropenem and linezolid, IVIG was given at a dose of 2 g/kg body weight, alongside methylprednisolone and enoxaparin were also given. However, at a later stage she started developing pulmonary edema and increased oxygen requirements, she was treated with tocilizumab (one dose of 12 mg/kg) on day 4 of hospitalization.

She was extubated on day 8 of hospitalization and gradually weaned off oxygen. She was discharged after a hospital stay of 20 days.

Table 1: Patient characteristics.

Variables	Patient 1	Patient 2	Patient 3
Age in years	8	7	10
Gender	Female	Male	Female
Time of presentation	4	2	4
SARS-CoV-2 testing (RT- PCR)	Positive	Positive	Negative
Laboratory values			
Leucocytes (K/µl) (4.5–13.5)	20.3	4.7	16.1

Continued.

Variables	Patient 1	Patient 2	Patient 3
Platelets (K/µl) (140–440)	243	286	283
Neutrophils (K/µl) (1.30–9)	16.04	18.04	4.42
Lymphocytes (K/µl) (1.90–7.5)	2.23	2.8	0.09
C-reactive protein (mg/L) (<9.9)	284.4	222	213
Erythrocyte sedimentation rate (mm/hour) (<20)	46	50	56
Fibrinogen (mg/dl) (183–503)	495	486	495
D-dimers (mcg/ml)	4.29	6	17.88
Ferritin (ng/ml) (13–145)	254	280	490
Albumin (g/dl) (3.8–5.4)	3.4	2.8	2.5
Creatinine (mg/dl) (0.6 to 1.3)	2.03	3.0	0.62
Troponin (ng/ml)	1.45	0.99	0.27
B-type natriuretic peptide (pg/ml)	383	389	1212
Chest imaging	Bilateral infiltrates	Bilateral infiltrates	Bilateral infiltrates with small pleural effusion
Transthoracic echocardiographic findings	No evidence of pulmonary hypertension. Trivial pericardial effusion	Hyperdynamic left ventricular systolic function; shortening fraction of 43%	Hyperdynamic left ventricular systolic function; shortening fraction of 40%
Duration of ICU stay in days	3	3	8

DISCUSSION

MIS-C is a newly recognized spectrum of disease manifestations in children associated with novel coronavirus SARS-CoV-2 infection.[4] MIS-C appears to be exclusively affecting children as per few published international reports published in peer reviewed journals.[5-7] This study is a report of 3 cases multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2 infection in New Jersey in three hospitalized patients from 04 April to 10 May 2020. All the children who were included to be a part of this study were aged between 6–10 years and were previously healthy within the range of normal body mass index (BMI) and without any comorbidities, who developed multi-organ involvement and systemic inflammation leading to critical illness needing intensive care.

Case reports of MIS-C which were first reported in children with United Kingdom (UK) , showed features of Kawasaki disease (KD) like illness was observed in children with COVID-19 in the late April and in a recent study it was reported that the children with cardiac involvement and shock had a higher mortality.[5,6] In another case report from Italy also described similar KD-like features in children with SARS-CoV-2 infection.[7] But there is paucity of data on the similar condition in various geographical areas.

The Centers for Disease Control and Prevention (CDC) has declared MIS-C to be a reportable illness as of 14 May 2020, and has provided a case definition which includes-patients under 21 years of age with fever (>38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours), laboratory evidence of inflammation [one or more of the following: elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes, and low albumin)], severe illness needing hospitalization, and involvement of two or more organ systems (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological), with positive testing for SARS-CoV-2 indicating current or recent infection or COVID-19 exposure; and no other alternative plausible diagnoses.[4]

Here in this present case series, all of our patients were compliant with the current case definition as given by CDC. All of them presented with multisystem disease with elevated inflammatory markers. Upon testing to detect SARS-CoV- 2 infection was positive in all patients.

The observations as a stated in a report from Italy described positive testing by RT-PCR and/or serology for SARS-CoV- 2 similar to our observation, but the observations made in the study from the UK, showed that all the children were antibody positive, but rest of the observations made were similar to our present study like, the evaluation for other infectious agents was found to be negative, all of our patients ended up in having a circulatory shock which warranted the use of inotropic support and all had elevated BNP and troponin levels.[5,7] However, one of our patients presented with neurologic involvement which has not been observed in published reports so far. All the children recovered with varying degrees of intensive care, respiratory support, inotropes, IVIG and steroids.[5-7]

One of our patients was covered with tocilizumab unlike previous reports of MIS-C. Though the usage of IL-6

though seen to be used in treating cases with COVID-19; however, their role in treatment of MIS-C needs to be further investigated. All the children have recovered and shown zero mortality has been reported in our study which was similar to the study from Italy.[7] All the children thus recovered were followed for recording any long-term complications.

CONCLUSION

Clinical presentation of MIS-C with multi-organ involvement and elevated inflammatory markers may have a presentation which is similar to the presentation as seen in Kawasaki disease and toxic shock syndrome. But now it has been presently understood to be a separate phenomenon and it has been related to a post-viral immune-mediated inflammatory process, and the pathogenesis of the occurrence of this syndrome complex still remains unclear.

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