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Case Series

Paediatrics Section

Paediatric Multisystem Inflammatory Syndrome Associated with COVID-19 Infection: A Case Series

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ABSTRACT

Multisystem Inflammatory Syndrome (MIS) is a newer, rarer and dangerous childhood disease that require early attention and is associated with Coronavirus Disease-2019 (COVID-19) infection. This article reports four clinically ill children of age 6-15 years admitted to Aster CMI Hospital, Bengaluru, Karnataka, India, during October and November 2020. The diagnosis was based on elevated laboratory values (D-Dimer, C-Reactive Protein (CRP), and Ferritin) and positive COVID-19 antibody test. No infectious aetiologies were identified. All patients presented at Emergency Room (ER) with hypotensive shock and were treated with inotropic support, Intravenous Immunoglobulin (IVIg), and steroids. Children responded well to treatment and were discharged within a period of 8-11 days. Clinical characteristics are necessary for understanding more about newly identified paediatric illness.

Keywords: Coronavirus disease-2019, Intravenous immunoglobulin, Multisystem inflammatory syndrome in children, Severe acute respiratory syndrome coronavirus-2

INTRODUCTION

As the COVID-19 continues to spread across the globe, a new inflammatory syndrome affecting multiple organ especially in children has been emerging in different countries. Reports from United Kingdom (UK), Italy and United States of America (USA) has described paediatric patients admitted to Intensive Care Unit (ICU) with severe inflammatory condition along with multiple organ failure and shock [1-3]. Exact pathophysiology of Multisystem Inflammatory Syndrome in Children (MIS-C) is unknown and yet to be identified, but is thought to be an exaggerated response of body's immune system. The hyper-inflammatory response induces decreased antiviral cytokines products and elevated inflammatory cytokines products, thus liberating huge inflammatory mediators along with hyperactive immune response, affecting both innate and acquired immunity. Limited data is available to suggest that the underlined condition is specific to children [4].

MIS-C is a condition that exhibit after or during the course of COVID-19 infection and is identified by hypotensive shock, fever, inflammation and multiple organ dysfunction. These features are similar to other inflammatory conditions like Kawasaki Disease (KD), Toxic Shock Syndrome (TSS) and macrophage activation syndrome [5].

As of 14th May 2020, MIS-C was declared to be a reportable illness by Center for Disease Control (CDC) [6] and has published a case definition which comprises an individual aged <21 years with:

- Body temperature ≥38°C for more than 24 hours.
- Serious conditions requiring hospitalisation.
- Multiple organ involvement (cardiac, renal, respiratory, rheumatology, gastrointestinal, dermatological, neurological).
- No other alternative diagnosis.
- Inflammatory evidences from Laboratory (elevated Erythrocyte Sedimentation Rate (ESR), fibrinogen, Lactate Dehydrogenase (LDH), CRP, ferritin, D-Dimer, Procalcitonin (PCT), or Interleukin-6 (IL-6); reduced lymphocytes or elevated neutrophils, low albumin).
- Diagnosed with COVID-19 infection currently or an exposure within four weeks prior to onset of symptoms.

Patients with this case definition must be reported by physicians to help their understanding and knowledge on risk factors, aetiology, diagnosis and treatment of this syndrome [6].

CASE SERIES

In accordance with CDC definition of MIS-C four clinically ill paediatric patients with the features of MIS-C are portrayed with their clinical features and management [Table/Fig-1].

Case 1

A 14-year-old male child reported with seven days of febrile illness, red eyes and macular rashes over legs. He presented in Emergency Room (ER) with hypotensive shock and respiratory distress. In view of positive COVID-19 IgG antibodies, patient was suspected for MIS-C and admitted to Paediatric Intensive Care Unit (PICU). Laboratory variables demonstrated a hike in sepsis markers, D-Dimer, ferritin, lactate, leucocytes, IL-6, cardiac markers and mild thrombocytopenia. His Echocardiogram (ECHO) revealed Left Ventricular (LV) dysfunction with a shortening Ejection Fraction (EF) of 40%. Ultrasound (USG) chest uncovered mild pleural effusion.

Treatment was started initially with IVIg, steroids and respiratory support was provided with High Flow Nasal Cannula (HFNC). His hospital stay was complicated by myocarditis which resolved with addition of milrinone and i.v. methylprednisolone. Supplements like carnitine, Coenzyme Q10 (CoQ10) and biotin were added to support cardiac function and hypoalbuminemia was treated with i.v. albumin infusion. The patient was discharged after 10 days of hospital stay.

Case 2

A eight-year-old child presented with complaints of four days of fever, abdominal pain, vomiting and melena. At the time of admission to ER child was in altered sensorium and had features of septic shock. His COVID-19 IgG and IgM antibodies were positive. Laboratory parameters showed thrombocytopenia, leukocytosis and elevated International Normalised Ratio (INR), D-Dimer, ferritin, sepsis markers and liver enzymes. USG abdomen revealed cortico-medullary changes with renal injury.

IV-Ig was the first line treatment given followed by steroids. In view of high liver enzymes and deranged coagulopathy vitamin K was added. Meropenam and teicoplanin were prescribed due to elevated sepsis markers. Respiratory support was provided using Humidified HFNC (HHFNC). Patient's hospital stay lasted for a duration of 11 days.

Parameters	Case 1	Case 2	Case 3	Case 4
Leucocyte (cells/L)	17,300	63,200	3,100	11,100
Platelet (cells/µL)	97,000	30,000	88,000	139,000
C-Reactive protein (mg/dL)	273.9	164.4	81.1	232
Procalcitonin (µg/L)	186.4	129.04	1.61	79
D-Dimer (ng/mL)	5321.66	67479	8854	3838.7
Ferritin (µg/L)	2187	3745	2291	651
Lactate dehydrogenase (U/L)	408	1271	NA	NA
Potassium (mmol/L)	3.14	6.89	3.4	2.5
Albumin (g/L)	NA	2.5	NA	2.5
Troponin (ng/L)	1190.1	NA	7.7	NA
CPK-MB (IU/L)	9.39	NA	0.80	NA
Interleukin-6	273	NA	NA	NA
Imaging results	ECHO – Myocarditis Ejection Fraction (EF)- 40% Chest X-ray-Mild pleural effusion observed	ECHO-normal	ECHO-EF-50%	ECHO-normal Chest X-ray-bilateral mild pleural effusion
Treatment	Noradrenalin, IVIg, Methylprednisolone, Enoxaparin Aldactone, Furosemide, Meropenam, Linezolid, Teicoplanin, Clindamycin, Ceftriaxone.	Noradrenalin, IVIg, Methylprednisolone, Amlodipine, Meropenam, Teicoplanin, Doxycycline, Piperacillin-tazobactum	Noradrenalin, IVIg, Methylprednisolone, Enoxaparin, Aspirin, Meropenem, Teicoplanin, Ceftriaxone	Noradrenalin, IVIg, Methylprednisolone, Aldactone, Ceftriaxone, Amikacin, Meropenem

[Table/Fig-1]: Diagnostic parameters and treatment.
ECHO: Echocardiogram

Case-3

A 15-year-old male child presented with four days of high grade fever, myalgia and macular rashes all over the body. On arrival to ER, he was in hypotensive shock and was noted to be drowsy and febrile with bounding pulses. His blood gas showed elevated lactate and was screened negative for COVID-19 gene expert but was positive for COVID-19 antibodies IgG and IgM, respectively. The child was having lymphopenia, elevated D-Dimer, ferritin and sepsis markers. ECHO test revealed dilated anterior descending artery with mild LV dysfunction (EF-50%). His troponin-I and Creatine Phosphokinase-Myocardial Band (CPK-MB) were marginally elevated initially and normalised later. Patient received IVIg, methylprednisolone, enoxaparin, aspirin and antibiotics. The length of stay of patient lasted for eight days and was discharged later on.

Case-4

A six-year-old child, previously healthy, presented with four days of febrile illness along with vomiting, abdominal pain, rashes and redness of eyes. On admission to ER, patient appeared flushed with conjunctival congestion, erythema of palm and redness of oral mucosa and lips. Child demonstrated tachycardia and hypotensive shock with bounding peripheral pulse. Patients COVID-19 IgG antibodies was positive suggesting of a recent COVID exposure. Laboratory values showed elevated D-Dimer, ferritin, and sepsis markers. Chest X-ray revealed bilateral mild pleural effusion.

He was started initially on IVIg He also received methylprednisolone for the signs of hyper inflammation. Hospital course was complicated by persistent hypokalemia, hypomagnesemia, and hypoalbuminemia which were treated with i.v. correction and albumin infusion. Pleural effusion and scrotal oedema responded to i.v. Furosemide. His hospital stay lasted for eight days.

DISCUSSION

This report is about four cases of MIS in children admitted in Aster CMI hospital during the month of October and November 2020. All patients admitted in PICU belonged to the age group of 6-15 years and had body weight varying from 18-58 Kg. Patient stayed in hospital for a duration of 8-11 days.

All the patients tested negative for COVID-19 gene expert but were positive for COVID-19 antibodies. All the four patients showed presence of IgG antibodies but only two had IgM antibodies which were similar to the reports from UK [1]. All patients initially presented at Emergency Room (ER) with hypotensive shock and among them two were noted to have respiratory depression. Fever was the common complaint in all patients, while three of them also presented with rashes and abdominal pain. Rashes were persistent throughout the body or restricted only over the legs. Vomiting, altered sensorium and drowsiness were the other complaints noted during the admission. These clinical findings were similar to studies from Mumbai and with CDC definition of MIS-C [6,7].

Patients were clinically assessed based on cardiac, sepsis and inflammatory markers, coagulation profile and ECHO. These tests guided to the assessment of organ involvement by MIS-C. Though patients presented with elevated laboratory values of inflammation and infection, no pathological organism was identified in all the index cases which was similar to other study reports [1,2] and CDC criteria of MIS-C [6]. Noradrenaline was started in the view of hypotensive shock and as patients became haemodynamically stable, it was tapered and finally stopped, persistent to study from UK [1]. ECHO and troponin level were used to assess cardiac function of the patients. Out of the four cases reported only one showed cardiac involvement with elevated troponin level and reduced EF of 40% whereas similar reports from UK, US and Mumbai demonstrated elevated troponin level and EF <50% [1,2,7].

IV-Ig served as first line choice in all the patients and methylprednisolone as second line. CRP and PCT levels approached normal range within 3 to 4 days of administration, indicating efficacy of IV-Ig and methylprednisolone to bring down inflammation [6-8]. In the UK and USA series ceftriaxone+clindamycin and ceftriaxone+linezolid served as the choice of antibiotics, respectively [1,2]. In present case series, empirical treatment for infection was provided using i.v. antibiotics meropenem+teicoplanin in most of the patients whereas only one patient received ceftriaxone+amikacin as initial choice. De-escalation of antibiotics was performed using ceftriaxone/piperacillin-tazobactam in view of negative culture report and declining sepsis markers within 4-6 days. Elevated D-Dimer, ferritin, as well as deranged coagulopathy was prescribed using enoxaparin with regular monitoring of platelet level. Choice of enoxaparin was based on its safety on paediatric age group [4] and clinical guidance published in American College of Rheumatology (ACR) [9].

As persistent fever was observed in all four patients acetaminophen was administered. Respiratory distress was treated by using HFNC

to restore oxygen saturation and breathe rate. Throughout the treatment plan i.v. correction was performed to maintain electrolyte levels. i.v. albumin infusion was given to normalise hypoalbuminemia in two patients. Supportive treatment was prescribed to achieve short term goals based on individual needs of patients and were consistent to international studies [1,2]. All of these patients were treated and discharged with no reported deaths as similar to reports from Italy [3].

CONCLUSION(S)

Multisystem Inflammatory Syndrome in Children (MIS-C) is a new disease and is observed as a separate entity though its features are conjoint to Kawasaki Disease (KD) and Toxic Shock Syndrome (TSS). Because of its idiopathic origin and unclear association with COVID-19 more about MIS-C spectrum will be known with increasing number of patients. Reporting of MIS-C will be key tool in understanding and controlling of the disease.

REFERENCES

[1] Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyper-inflammatory shock in children during COVID-19 pandemic. The Lancet. 2020;395(10237):1607-08.
[2] Kest H, Kaushik A, DeBruin W, Colletti M, Goldberg D. Multisystem inflammatory syndrome in children associated with 2019 Novel Coronavirus (SARS-CoV-2) Infection. Hindawi. 2020;10(1155):01-04.
[3] Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Cuiffredo M, et al. An outbreak of severe Kawasaki-like disease at the Italian epicenter of the SARS-CoV-2 epidemic: An observational cohort study. Ee Lancet. 2020;395(10239):1771-78.
[4] Simon H, Sakano TMS, Rodriguez RM, Eisencraft AP, De Carvalho VEL, Schvartsman C, et al. Multisystem inflammatory syndrome associated with COVID-19 from the pediatric emergency physician's point of view. Journal de Pediatria. 2020;10(1016):01-20.
[5] Royal College of Paediatrics and Child Health Guidance "Paediatric multisystem inflammatory syndrome temporally associated with COVID-19," 2020, https://www.rcpch.ac.uk/resources/guidance-paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19.
[6] Centers for Disease Control and Prevention (CDC), "Health advisory on multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019," 2019, https://emergency.cdc.gov/han/2020/han00432.asp.
[7] Jain S, Sen S, Lakshmivenkateshiah S, Bobhate P, Venkatesh S, Udani S, et al. Multisystem inflammatory syndrome in children with COVID-19 in Mumbai, India. Indian Pediatrics. 2020;57(11):1015-19.
[8] Mastuda EM, Dos Santos SA, Castejon MJ, Ahagon CM, De Campos IB, De Macedo Brigido LF. COVID-19 in children: A case report of Multisystrem Inflammatory Syndrome (MIS-C) in Sao Paulo, Brazil. Braz J Infect Dis. 2020;24(6):580-82.
[9] American College of Rheumatology," Clinical Guidance for Pediatric Patient with Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with SARS-CoV-2 and Hyperinflammation in COVID-19",2020, https://www.rheumatology.org/Portals/0/Files/ACR-COVID-19-Clinical-Guidance-Summary-MIS-C-Hyperinflammation.pdf.

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