MIS-C sequel to COVID-19 infection, diagnostic challenge and management. A case report

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ABSTRACT

Multisystem inflammatory syndrome in children (MIS-C) is a rare sequel to severe acute respiratory syndrome coronavirus (SARS-CoV-2). Clinical picture of MIS-C includes multi system inflammation alongside fever and severe illness with laboratory evidence of raised inflammatory markers. MIS-C may resemble toxic shock syndrome, complete or incomplete Kawasaki disease and macrophage activation syndrome. Actual management of MIS-C is yet to be formulated, currently treatment is supportive only. In addition, as MIS-C is a new clinical entity we do not know about its long-term prognosis.

Keywords: COVID-19, diagnosis, MISC-C,

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INTRODUCTION

Multisystem Inflammatory Syndrome in Children (MIS-C) is a condition that is characterized by fever, inflammation and multi-organ dysfunction and manifests several weeks after the infection of SARS-CoV-2[1]. Since the declaration of COVID 19 as global pandemic doctors, health workers, and researchers have been working day in and day out to study its clinical features, manifestation and management. COVID-19 has attributed to 2,424,060 death as of February 2021[1]. Children represented 13.0% of total cumulated cases in United States reporting cases by age. As per American academy of pediatrics, available data indicated that COVID-19-associated hospitalization and death is uncommon in children[2]. On May 14, the CDC released a Health Advisory on a severe life-threatening complication of pediatric COVID-19 termed Multisystem Inflammatory Syndrome in Children (MIS-C) [3]. Nepal had reported the first death of a child from the 'multisystem inflammatory syndrome in children' (MIS-C) on December 22, 2020 that is believed to be induced by Covid-19[4] which is backed up by the fact to consider MIS-C in any pediatric death with the evidence of SARS-CoV-2 infection as per CDC 2020. Here we describe the first case of MIS-C diagnosed and managed in Patan Academy of Health Sciences (PAHS), Patan Hospital, Lagankhel, Nepal.

CASE REPORT

A 13 years previously healthy adolescent girl presented to Emergency department with history of high-grade fever for 4 days. She also had history of vomiting, loose stool, myalgia, and easy fatigability for same duration. There was history of altered sensorium, rashes over the face and body and cracked lips for 2 days. She had travel history to a COVID hotspot 2 weeks back however, she was not checked for SARS COVID. On admission, she was sick looking and drowsy with GCS of 12/15. She was pale, febrile with temperature of 102 °F, tachypneic with respiratory rate of 34 breaths per minute with SPO2 of 97% in room air. She had tachycardia with heart rate of 150 beats per minute with cold peripheries, CRT of >3 seconds, feeble pulses and hypotension with blood pressure of 60/30 mm of Hg. The rest of the systemic examination was normal. The initial management was done in COVID ER with intravenous crystalloid boluses (bolus of 20 ml /kg, three times a total of 60 mL/kg), 1st dose of intravenous broad-spectrum antibiotics (inj ceftriaxone, inj vancomycin and inj clindamycin) after sending investigations and cultures. She was then shifted to COVID PICU with differential diagnosis of toxic shock syndrome (TSS), Kawasaki disease (KD), septic shock and MIS-C. As she had hypotension despite 3 fluid boluses, she was started on inotropes in PICU. Empirical antibiotics (ceftriaxone and vancomycin) was started. Clindamycin was added for TSS. In view of MIS-C, parents were counselled regarding starting IVIG, but due to financial constraints, IVIG could not be given.

Investigations revealed elevated WBC (16700 cells/ul) count with neutrophilia (Neutrophil=85%), lymphopenia (lymphocyte 15%) , thrombocytopenia (platelets = 70000/ul) and low hemoglobin (Hb= 7.6 mg/dl), elevated inflammatory markers, including: C-reactive protein (270 mg/l), erythrocyte sedimentation rate (64 mm in first hour), ferritin (1000 ng/ml), elevated cardiac markers – Troponin I (positive) , Hypoalbuminemia (2.1 g/dl), elevated lactate dehydrogenase (330 iu/l), hypertriglyceridemia (259 mg/dl). RT-PCR for COVID-19 was negative but COVID antibody was positive. Blood culture and urine culture were negative. At the same time her mother tested positive for COVID-19 during contact tracing. Chest radiograph showed small pleural effusion, patchy consolidations, focal consolidation, and atelectasis or nodular ground-glass opacification on right side. USG abdomen revealed free fluid, ascites, and bowel and mesenteric inflammation including terminal ileitis, mesenteric adenopathy/adenitis, and peri-cholecystic edema. Echocardiography showed mild concentric LVH, mild TR with normal PAP, normal LV systolic and diastolic function (EF=60%), minimal pericardial effusion, no intracardiac mass, thrombus and vegetations.

Reviewing the history, clinical features and investigations, the diagnosis of MIS-C was made in this child. We started corticosteroid on 4th day of admission in this child as COVID antibody titer was positive and they could not afford IVIG. She gradually improved on above treatment and was shifted to non-COVID PICU after 2 consecutive negative PCR reports. She was then transferred to children ward after 9 days. At children ward, she developed delirium and irrelevant talks and abnormal behavior for which psychiatric consultation was done. She was diagnosed as acute delirium and prescribed oral quetiapine for 7 days. she received total 18 days course of IV antibiotics including ceftriaxone for 4 days, chloramphenicol for 7 days, vancomycin for 8 days, clindamycin for 10 days, linezolid for 10 days and meropenem for 7 days. Her symptoms gradually improved and she was discharged after 19 days of admission with normal neurological

examination. She was discharged on oral iron tablet for low hemoglobin. On consecutive follow up she had normal echo finding and normal hemoglobin.

- An individual aged <21 years presenting with fever*, laboratory evidence of inflammation**, and evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); AND
- No alternative plausible diagnoses; AND
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms.

*Fever >38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours
**Including, but not limited to, one or more of the following: an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin.

Additional comments:
- Some individuals may fulfill full or partial criteria for Kawasaki disease but should be reported if they meet the case definition for MIS-C.
- Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection.

Figure 1. Case definition of MIS-C as per CDC[6]

DISCUSSION

The MIS-C initially was also termed as post-inflammatory multisystem syndrome temporally associated with SARS-CoV2 infection (PIMS-TS).The clinical presentation of MIS-C includes fever, severe illness, and the involvement of two or more organ systems, in combination with laboratory evidence of inflammation and laboratory or epidemiologic evidence of SARS-CoV-2 infection[7]. Some features of MIS-C resemble Kawasaki disease, toxic shock syndrome, and secondary hemophagocytic lymphohistiocytosis/ macrophage activation syndrome.[7] The incidence of MIS-C is yet uncertain; it is a rare complication of COVID-19. From March 1 through May 10, 2020, the incidence of laboratory-confirmed SARS-CoV-2 infection was 322 per 100,000 persons younger than 21 years of age, and the incidence of MIS-C was 2 per 100,000 persons younger than 21 years of age[8]. The pathophysiology of MIS-C is not well understood. It has been suggested that the syndrome results from abnormal immune response to the virus, likely due to sustained cytokine storm. One of the key concerns about MIS-C is its close resemblance with Kawasaki disease. There are several important features of MIS-C that differentiate it from Kawasaki disease, recent data indicate that coronary artery dilation in patients with MIS-C is mild and transient.[9]

Treatment of patient with MIS-C is based on the clinical presentation. Our patient had persistent fever, gastrointestinal symptoms (vomiting and diarrhea), rashes, mucus involvement, altered mental status, respiratory symptom (tachypnea). On clinical examination, she was in shock, with features suggestive of septic shock. The multisystem nature of MIS-C has invited a multidisciplinary approach to management, including intensivists, infectious disease pediatricians, rheumatologists, cardiologists and hematologists, surgeons (where acute abdominal conditions are suspected) and specialist nurses[10]. Patient with MIS-C should be resuscitated accordingly with fluid and inotropes, if necessary, as was done with our patient who presented in shock. Similarly, patient with features suggestive of MIS-C is treated with intravenous immunoglobin (IVIG), which was not done in our patient due to affordability issue. Patient should be treated with empirical antibiotic at presentation according to local institutional protocol, which needs to be discontinued once bacterial infection has been ruled out. The role of SARS-CoV-2 antiviral therapies in the management of MIS-C is still uncertain. Glucocorticoid therapy can be given initially intravenously i.e. methylprednisolone at a dose of 12 mg/kg/day in two divided dose, and needs to be tapered off when patient has defervesced[11]. Antithrombotic therapy like low dose aspirin, enoxaparin is warranted in many cases to prevent thrombotic complication. Other adjunctive (glucocorticoids) and immunotherapy (IL-1/IL-6 inhibitors and convalescent plasma) role has yet to be established in the management.

Since the MIS-C is a new clinical entity, the long-term prognosis is uncertain. Nevertheless, we must be vigilant in any patients with current or prior history of COVID infection meeting case definition of MIS-C. Similarly, any patient with symptoms of Kawasaki disease and/ or toxic shock

syndrome with the history of past or present COVID infection should be suspected of MIS-C.

REFERENCES

1. World Health Organization. WHO Coronavirus Disease (COVID-19) Dashboard. World Health Organization [Internet]. Weblink [Accessed February 19, 2021]
2. American Academy of Pediatrics: Children and COVID-19: State-level data report. American Academy of Pediatrics [Internet]. Critical Updates on COVID-19. Weblink [Accessed February 19, 2021]
3. Greene AG, Saleh M, Roseman E, Sinert R. Toxic shock-like syndrome and COVID-19: multisystem inflammatory syndrome in children (MIS-C). Am J Emerg Med. 2020;38(11):2492.e5-6. DOI
4. Online Khabar. Nepal reports first death from MIS-C induced by Covid-19. Online Khabar (English) [Internet]. News; 22 Dec 2020. Weblink [Accessed February 19, 2021]
5. Streptococcal Toxic Shock Syndrome | 2010 Case Definition.
6. Centers for Disease Control and Prevention. Emergency preparedness and response: Health Alert Network, Archive - 00432 [Internet]. Centers for Disease Control and Prevention. HAN00432; 14 May 2020. Weblink [Accessed February 21, 2021]
7. Nakra NA, Blumberg DA, Herrera-Guerra A, Lakshminrusimha S. Multi-system inflammatory syndrome in children (MIS-C) following SARS-CoV-2 infection: review of clinical presentation, hypothetical pathogenesis, and proposed management. Children (Basel). 2020;7(7):69. DOI
8. Dufort EM, Koumans EH, Chow EJ, Rosenthal EM, Muse A, Rowlands J, et al. Multisystem inflammatory syndrome in children in New York State. N Engl J Med. 2020;383(4):347-58. DOI
9. Rowley AH, Shulman ST, Arditi M. Immune pathogenesis of COVID-19–related multisystem inflammatory syndrome in children. J Clin Invest. 2020;130(11):5619-21. DOI
10. Carter MJ, Shankar-Hari M, Tibby SM. Paediatric inflammatory multisystem syndrome temporally-associated with SARS-CoV-2 infection: an overview. Intensive Care Med. 2021;47(1):90-3. DOI
11. Henderson LA, Canna SW, Friedman KG, Gorelik M, Lapidus SK, Bassiri H, et al. American College of Rheumatology clinical guidance for multisystem inflammatory syndrome in children associated with SARS–CoV-2 and hyperinflammation in pediatric COVID-19: version 1. Arthritis Rheumatol. 2020;72(11):1791-1805. DOI