CASE SERIES

Multisystem Inflammatory Syndrome In Children (MIS-C): A Case Series in a Tertiary Hospital

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ABSTRACT

The clinical course of COVID-19 in the pediatric population has been reported to be mild in the majority of affected patients. However, a condition referred to as multisystem inflammatory syndrome in children (MIS-C) can occur with SARS-CoV-2 infection where patients can become critically ill. In this series, we describe five pediatric patients with the spectrum of MIS-C associated with SARS-CoV-2 infection.

KEYWORDS: *MIS-C, COVID-19, SARS-CoV-2*

INTRODUCTION

Coronavirus disease 2019 (COVID-19) was first reported in Wuhan, China and since then has spread throughout the world causing an unprecedented pandemic in March 2020. The clinical course of COVID-19 in the pediatric population has been mild, but some children infected with SARS-CoV-2 can be critically ill due to multisystem inflammatory syndrome in children (MIS-C).

The World Health Organization (WHO) has provided a case definition of MIS-C which must meet six criteria: (1) patients 0-19 years of age, (2) fever ≥3 days, (3) at least two clinical signs of multisystemic involvement (rash, conjunctivitis, hypotension, cardiac dysfunction, evidence of coagulopathy, gastrointestinal symptoms), (4) elevated inflammatory markers (eg, ESR, CRP or procalcitonin), (5) no other obvious cause of inflammation, and (6) evidence of SARS-CoV-2 infection either by exposure to a confirmed case or a positive SARS-CoV-2 RT PCR, serology or antigen test.[1]

In this case series, we describe five pediatric patients with the spectrum of MIS-C associated with SARS-CoV-2 infection.

PATIENTS' INFORMATION

Five children aged 17 months to 12 years with features of Kawasaki Disease (KD) and who are positive for SARS-CoV-2 are presented. All patients were previously healthy with no comorbidities.

CASE PRESENTATION

Case 1: A 12-year old male presented with a 9-day history of fever, bilateral eye redness, pruritic, erythematous rashes and vomiting. Dengue was ruled out and the patient was given an unrecalled antibiotic. Two days prior to admission, fever was accompanied by diarrhea with generalized, crampy abdominal pain, decreased appetite and activity. On the day of admission, there was persistence of symptoms with body malaise. He was brought to a local hospital where the following laboratory tests were done: CBC showed a WBC of 25.8 x10^9/L, segmenters of 86.2% and platelet count of 500x10^9/L. Urinalysis showed a WBC of 5-10/hpf. Serum sodium was 130 mmol/L and potassium was 2.9 mmol/L. The patient was subsequently transferred to our institution. There were no sick contacts nor exposure to COVID-19 confirmed cases.

The patient was seen weak-looking and dehydrated with the following vital signs: BP of 90/60 mmHg, HR 145 breaths/min, RR 30 breaths/min and temperature of 38.6°C. On physical examination, there was conjunctival injection, hyperpigmented macules on bilateral lower extremities with weak pulses, cold extremities, and capillary refill time (CRT) > 2 seconds. Assessment was compensated shock secondary to infectious diarrhea, to consider typhoid fever; COVID-19 suspect. Blood tests revealed a WBC of 28.4 x 10^9/L, segmenters at 89% and procalcitonin at 9.992ug/L (20x). Serum potassium was 2.9 mmol/L and calcium was 2.17 mmol/L. Blood, stool and urine cultures were negative. Ceftriaxone was given at 100 mg/kg/day IV once daily. SARS-CoV-2 RT-PCR nasopharyngeal and oropharyngeal swabs were positive for viral RNA with a Cycle threshold (Ct) value for N Gene of 36.94 and ORF1ab of 0.00 done.

Despite several courses of antibiotics, patient remained to have high grade fever, with loose stools, abdominal pain and anorexia. Inflammatory markers showed an ESR of 115 mm/hour (5x elevated), CRP of 110 mg/L (110x elevated) and ferritin of 772 ng/mL (2x elevated). A diagnosis of MIS-C was considered. IVIG 2 g/kg/dose for 12 hours and Aspirin 80 mg/kg/day orally every 6 hours were given on the 16th hospital day. Fever resolved after 36 hours of IVIG. ASA therapy at 5 mg/kg/dose once daily orally was continued. Repeat SARS-CoV-2 RT PCR result was negative after 14 days. There was diffuse coronary arteritis on 2D-echocardiogram which was done on the 17th hospital day. On the 22nd hospital day, he was sent home improved with home medication of aspirin at 5 mg/kg/dose once a day orally until follow up with the cardiologist.

Case 2: A 17-month-old female presented with a 9-day history of high-grade fever and decreased appetite and activity. She subsequently developed bilateral eye redness with periorbital edema, dry, red, cracked lips, intermittent episodes of vomiting, diarrhea, and productive cough.

On admission, impression was complete Kawasaki Disease, pneumonia, COVID-19 suspect. On physical exam, the patient had fever, bilateral conjunctival injection, erythematous, cracked lips, a unilateral 2-cm cervical lymphadenopathy, perineal desquamation, and bipedal edema. Chest radiograph showed mild pulmonary underinflation. CBC showed a

hemoglobin of 81 g/L, WBC of 12.3 x 10^9/L, neutrophils of 76%, and a platelet count of 297 x 10^9/L. Blood culture was negative. Serum AST was 46 U/L, with normal ALT, and albumin was 27.5 g/L. Inflammatory markers showed a CRP of 226 mg/dL, ESR of 65 mm/hr, procalcitonin of 11.57 ug/L, and ferritin of 1064 ng/mL. 1 dose of IVIG at 2 g/kg and aspirin at 90 mg/kg/day for 24 hours were given and fever immediately resolved within the 1st hour of IVIG infusion. SARS-CoV-2 RT-PCR nasopharyngeal and oropharyngeal swab done on the 9th day was positive with Ct values for N Gene of 37.78 and ORF1ab of 0.00. A 2d-echocardiogram was requested but was not done during the admission since the swab result was still pending. She was discharged on low-dose aspirin and was advised to do strict isolation. The caregiver and the local epidemiologic surveillance unit was informed when the SARS-CoV-2 RT-PCR nasopharyngeal and oropharyngeal swabs turned out positive.

Case 3: An 11-year-old female presented with a 6-day history of fever and nonpruritic, maculopapular rashes over the extremities. She was initially admitted at another hospital on the 3rd day of fever and laboratories showed a WBC count of 15.1 x 10^9/L with segmenters of 84%, lymphocytes of 7%, CRP of 49.5 mg/dL, and a positive serology for dengue IgG and IgM. Her chest radiograph was normal. Due to hypotension and persistence of fever, the patient was transferred to our institution.

At the triage, the patient had the following vital signs: BP 70/40 mmHg, HR 130 beats/min, RR 30 breaths/min and temperature of 36.7°C. She had non-blanching, urticarial rashes over the extremities with bilateral subconjunctival hemorrhages. Fluid resuscitation and inotropes were started. Chest radiograph showed right pleural effusion with intercurrent pneumonia. She was given oxygen support and was eventually intubated due to respiratory failure. Inflammatory markers were as follows: procalcitonin 1.708 ng/mL, serum ferritin 472 ng/mL, LDH 282 mg/dL and CRP 259 mg/dL.

SARS-CoV-2 RT-PCR nasopharyngeal and oropharyngeal swabs on the 8th day of illness was positive with a Ct value of N Gene: 30.63 and ORF1ab: 32.18. IVIG at 2g/kg over 12 hours and dexamethasone at 0.15mg/kg once daily were given. Piperacillin-tazobactam was started for hospital-acquired pneumonia. Nutritional support with 20mg elemental zinc 2x daily and 2,000 IU/day of vitamin D3 were given.

Despite aggressive supportive and medical management, she remained hemodynamically unstable, with episodes of hypotension, and fever (37.8-39.5°C). Her sensorium quickly deteriorated on the 5th hospital day. On the 6th hospital day (12th day of illness), laboratories were as follows: prothrombin time 104sec, INR 8.71, D-dimer 10 ng/dL, CRP 45.5 mg/dL, LDH 37,562 mg/dL, procalcitonin 2.35 ng/mL, and serum ferritin 89,390 ng/mL. Blood cultures were negative. Hemoperfusion was considered, however, patient remained unstable. On the 16th day of illness, pulse methylprednisolone was given at 0.8mg/kg IV once daily, but the patient succumbed on the 17th day of illness.

Case 4: A 9-year-old female presented with a 4-day history of fever, diarrhea, tender left cervical lymphadenopathy, hematuria, anorexia and nonsuppurative bilateral conjunctivitis with dyspnea.

At the triage, she was febrile and in compensated shock. She was immediately intubated and started on inotropes. On physical examination, she had red, moist lips, with a 1-cm left tender cervical lymphadenopathy and a 2-cm occipital lymphadenopathy. She had clear and equal breath sounds but had marked intercostal and subcostal retractions. Abdomen was soft, flat with direct epigastric tenderness. Her chest radiograph showed pneumonia. SARS-CoV-2 RT-PCR nasopharyngeal and oropharyngeal swabs on 2 different occasions taken 3 days apart were both negative. Ceftriaxone was started for pneumonia and IVIG at 2g/kg as a 12 hour infusion was given. Pertinent laboratories were as follows: WBC 19.8 x 10^9/L, segmenters 93%, lymphocytes 6%, platelet count 131 x 10^9/L, CRP 139mg/dL, and ferritin 2,907ng/mL.

Despite medical and supportive management, the patient did not tolerate weaning from mechanical ventilation. From the COVID-19 ward, she was eventually transferred to the Pediatric Intensive Care Unit on the 8th hospital day (12th day of illness). MIS-C was highly considered and SARS-CoV-2 antibody determination using electro-chemiluminescence immunoassays (ECLIA) was done. The result was positive for SARS-CoV-2 immunoglobulin G antibody. Nutritional support with zinc sulfate at 20mg elemental zinc 2x daily and vitamin D3 at 2,000 IU/day were given. Other supportive management were adequate fluids, titration of inotropes

and rapid weaning from mechanical ventilation. She was successfully extubated on the 12th hospital day. A 2D-echocardiogram was done on the 13th hospital day (18th day of illness) showing minimal pericardial effusion. She was eventually discharged improved on the 15th hospital day (20th day of illness).

Case 5: An 8-year-old female presented with a 4-day history of fever with dizziness, vague, generalized abdominal pain, conjunctival injection, headache and myalgia. She was diagnosed to have tonsillitis on two occasions by a pediatrician and was given antibiotics without improvement. Two days prior to her admission, she developed erythematous patches over the hands, feet, knees and abdomen associated with diarrhea.

At the triage, vital signs were BP 60/40 mmHg, RR 65 breaths/min, HR 139 beats/min, temperature 39.7°C, with an O_2 saturation of 97%. She had conjunctivitis with perilimbal sparing. Non-tender, bilateral cervical lymph nodes were palpated which measured <1 cm in size. Crackles were appreciated on auscultation. There were erythematous patches on the abdomen, knees, palms and soles.

Laboratory results were as follows: CBC: WBC 27,000/µL, segmenters 95%, CRP 508 mg/dL, procalcitonin 95.2 µg/L, and serum ferritin 959.3 ng/mL. Liver function tests were normal but the BUN was at 16.3 mmol/L and creatinine was at 143 µmol/L. The chest radiograph showed reticulonodular densities scattered throughout both lungs, predominantly in the bilateral inner lung zones suggestive of pneumonia. Ceftriaxone 100 mg/kg/day and vancomycin 60 mg/kg/day were started. SARS-CoV-2 RT PCR was negative. MIS-C was highly considered and IVIG dose was given.

SARS-CoV-2 antibody testing using ECLIA was requested on the 5th hospital day (9th day of illness) with positive titers for both for IgG and IgM titers. A 2D-echocardiogram showed biventricular dysfunction with an ejection fraction of 18%, moderate mitral regurgitation, tricuspid regurgitation, mild aortic regurgitation, and pulmonic regurgitation. She was discharged on the 20th hospital day after completing treatment for healthcare-associated pneumonia.

DISCUSSION

The United Kingdom reported the first case series of a mysterious disease in eight children who exhibited mild symptoms with Kawasaki-like features at a tertiary center in South East England[2] last April, 2020. This condition was later called Pediatric Multisystem Inflammatory Syndrome (PMIS). Since then, reports in a number of cases with hyperinflammatory shock with phenotypic presentation of KD emerged in other parts of the world, including South Africa, Canada and the United States[1,3-5]. When it was reported in the United States, it was subsequently termed as Multisystemic Inflammatory Syndrome in Children (MIS-C). In several case reports, there have been overlapping features of KD and MIS-C but unlike KD which is predominantly seen in children of Asian descent, reports of MIS-C is scarce from Asian countries during the early parts of the pandemic[5,6]. Although many children met the criteria of either classic or incomplete KD, the epidemiology of both diseases is different. MIS-C occurs in older children with a median age of 8 to 11 years (range 1-20 years old)[7] and those belonging to the younger age group presented with worse clinical outcomes. Recently, rare cases of multisystem inflammatory syndrome associated with SARS-CoV-2 have been reported in adults (MIS-A)[8].

MIS-C can be seen in both children and adolescents. All our patients, aged 17 months to 12 years, were previously healthy with no comorbidities but presented with Kawasaki-like features including conjunctivitis, rashes and mucositis. All presented with signs of shock upon admission. They all met the WHO criteria for MIS-C with all five cases presenting with fever of more than 3 days duration. In a case series by Feldstein, et al., which included 186 patients, 78% had fever of more than 5 days, 12% had fever of 4 days while the remaining had fever of 3 days duration.[5] Four of our patients presented with gastrointestinal symptoms like diarrhea, vomiting, anorexia and abdominal pain. Compared to COVID-19, gastrointestinal signs and symptoms appear as a more prominent feature of MIS-C. [9,10]

Like Kawasaki disease, MIS-C can also present with cardiac dysfunction. Patients 1, 4 and 5 had 2D-echocardiogram findings of arteritis, pericardial effusion and valvular regurgitation, respectively. These findings associated with MIS-C are not uncommon. In a large case report by Godfred-Cato, et al., [11] involving 203 patients with clinical course consistent with MIS-C, approximately 30-40% of children had depressed left ventricular function and 8-19% had coronary artery abnormalities. Since MIS-C is an emerging disease with unknown long-

term sequelae, the occurrence of coronary involvement in association to MIS-C remains to be elucidated.

Some of the laboratory features of MIS-C strongly resemble those of hemophagocytic lymphohistiocytosis (HLH) or macrophage activation syndrome (MAS). Majority of our MIS-C cases have markedly elevated inflammatory markers on admission, such as C-reactive protein, procalcitonin, ferritin, and LDH. Among the five cases, the third case with refractory shock had an extremely high ferritin value (89,390 ng/mL from baseline of 472ng/mL), high LDH (37,562 mg/dL from baseline of 282mg/dL), lower platelet count (130 x 10^9/L), and lower serum albumin compared with the other cases. Viral infections are well-known triggers of HLH or MAS.[12,13] It is characterized by a robust immune response leading to cellular activation and "cytokine storm" but with inability to eliminate the antigenic stimuli.[14,15] Whether the third case ultimately developed HLH is difficult to establish as it is a rare, but potentially fatal disorder that can mimic MIS-C.

The interval between infection and development of MIS-C is unclear. Belot et al., reported that MIS-C was seen 4-5 weeks after the peak of COVID-19 cases in the country.[16] All our patients presented in the emergency department from June to September, which also occurred more than 4 weeks from the peak of COVID-19 cases in the Philippines. All 5 patients had a 4 to 9-day history of fever and one was critical and unstable on admission. Whether the patient (case 3) was a case of MIS-C or severe COVID-19 is hard to tell based on clinical presentation. We reviewed the Cycle threshold (Ct) values for N Gene and ORF1ab since prolonged Ct values (range 30.8-41.7) may be correlated with less cultivable virus.[17,18] Her results were 30.63 and 32.18, respectively.

MIS-C is a life-threatening post-infectious complication occurring unpredictably weeks after mild or asymptomatic SARS-CoV2 infection in otherwise healthy children[19] although the pathogenesis of the syndrome remains largely unclear. Patients with MIS-C can either have a positive RT-PCR or serology. Patients 1, 2 and 3 tested positive for SARS-CoV-2 on RT-PCR between the 8th to 12th day of illness. Although SARS-CoV-2 RT-PCR was negative, patients 4 and 5 tested positive for SARS-CoV-2 IgG using ECLIA taken on the 5th and on the 14th day of illness, respectively. These tests are crucial to augment clinical diagnosis and guide treatment.

The rationale for the use of IVIG and systemic steroids in SARS-CoV-2 infection is modulation of inflammation. Four of our patients had good response with resolution of fever after being given one dose of intravenous immunoglobulin (IVIG) given at 2g/kg. Patient 3 showed poor response to a single dose of IVIG, thus, additional doses at 1g/kg/day was given for the next 4 days. Dexamethasone was given for severe pneumonia at 0.15mg/kg/dose to patients 3, 4 and 5. Patient 3 received an additional dose of pulse methylprednisolone, after completion of a 10-day course of dexamethasone, because of worsening symptoms.

During the hospital admission of these MIS-C cases, the role of aspirin in MIS-C was not yet clearly defined. Patients 1 and 2 were treated with the standard therapy used for Kawasaki Disease, such as IVIG and aspirin at a dose of 80 mg/kg/day divided every 6 hours orally until patient was afebrile for at least 48 hours. Aspirin was subsequently shifted to anti-thrombotic doses at 3-5 mg/kg/day once daily. Aspirin has anti-inflammatory and anti-platelet properties which are believed to be the result of peripheral inhibition of COX-1 and COX-2. In one institutional protocol, aspirin 20 to 25 mg/kg/dose every 6 hours (80-100 mg/kg/day) is recommended in patients with MIS-C with Kawasaki disease-like illness, evidence of excessive inflammation (ferritin >700 ng/ml, CRP >30 g/dL, or multisystem organ failure), or cardiac involvement.[20] According to the American Academy of Pediatrics Multisystem Inflammatory Syndrome in Children Interim Guidance, all patients with MIS-C, unless with contraindications (e.g., platelets <100,000 or active bleeding), should be started on low-dose aspirin for thromboprophylaxis.[21]

Managing MIS-C requires a multidisciplinary team hence timing of subspecialty referral is crucial. Majority of the cases upon admission, were immediately referred to a pediatric intensivist on the first episode of shock. Since most patients presented with KD-like illness, all patients were referred to cardiology service for evaluation. Due to unavailability of the 2D-echocardiogram machine inside the COVID-19 ward, echocardiography was done when patients were no longer considered infectious. Either way, management for MIS-C was ultimately based on both clinical and diagnostic results, and management did not change whether or not a 2D-echocardiogram was done earlier.

Except for patient 3, all patients were discharged improved. Consent for publication was obtained prior to writing this case series.

CONCLUSION

We observed five cases of multisystem inflammatory syndrome in children (MIS-C) in previously healthy patients with SARS-CoV-2 infection. Children with this condition decompensate quickly and most will require intensive care unit admission. It is important to emphasize the need for families to seek immediate medical care since early diagnosis and timely intervention is imperative.

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