Multisystem Inflammatory Syndrome in Children*

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ABSTRACT

Multisystem inflammatory syndrome in children (MIS-C) is a condition which is associated with Coronavirus that mimics Kawasaki Disease (KD) where organ dysfunction is evident which includes the heart, lungs, kidneys, brain, skin, eyes, or gastrointestinal organs.

This report describes the first case of Multisystem Inflammatory Syndrome in children in Region 1. Our patient is a 3 year old female who presented with sudden onset of high grade fever, abdominal pain and diarrhea, a month after recovering from COVID-19 infection. On admission, the patient was irritable, febrile with conjunctival erythema, reddish dry lips, slightly distended and non-tender abdomen, erythematous rash over umbilicus, feet and hands, minimal edema of hands and feet. Laboratories requested showed elevated inflammatory markers, elevated BNP, Troponin I, elevated D-dimer, fibrinogen and prolonged activated partial thromboplastin time (APTT) and prothrombin time (PT) (Appendix A,B,C,H). 2D-echocardiography showed left ventricular dysfunction, moderate mitral regurgitation, minimal pericardial effusion and right coronary artery ectasia (Appendix F). On second hospital day, she had hypotension hence was transferred to Intensive Care Unit which required initiation of inotropes and close care monitoring. Intravenous Immunoglobulin (IVIg) and corticosteroids were also started. She was discharged stable and improved on seventh hospital day with a repeat 2D-echocardiogram showing improved left ventricular function and decrease in right coronary artery dilation.

Prompt recognition of this syndrome allows clinicians to acquire appropriate laboratory testing, initiate treatment and provide families with accurate prognostic information.

Keywords: Multisystem Inflammatory Syndrome, COVID-19, Intravenous immunoglobulin

OBJECTIVES

1. To present a case of Multisystem Inflammatory Syndrome in children.
2. To present the incidence of Multisystem Inflammatory Syndrome
3. To discuss the clinical features, causes, criteria, treatment and outcome of MIS-C.

INTRODUCTION

On December 31, 2019 the World Health Organization reported cases of pneumonia of unknown cause in Wuhan City, China. A novel coronavirus was identified as the cause by Chinese authorities on 7 January 2020 and was named "2019-nCoV".

The World Health Organization has designated the disease COVID-19, which stands for coronavirus disease 2019. The virus that causes COVID-19 is designated severe acute respiratory syndrome coronavirus 2 (SARS-Cov 2).

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In children, COVID-9 is generally mild. However, in rare cases, children maybe critically affected, and medical manifestations may also vary from adults (1). Multisystem Inflammatory Syndrome in children is a rare complication associated to COVID-19 infection presented as high grade fever, elevated inflammatory markers and organ dysfunction occurring 4-6 weeks after infection (5). The incidence of MIS-C is uncertain, occuring <1% of children with previously infected confirmed SARS-CoV-2 infection

CASE

This is a case of a 3 year old female who was admitted due to fever. History started five weeks prior to admission, when the patient was exposed to a COVID-19 confirmed patient, she was subjected to COVID RT-PCR which turned out positive. She was admitted at a local isolation facility in which she exhibited loose stools for 1 -2 days without other accompanying symptoms. A repeat RT-PCR was done on tenth day of illness which turned out negative.

On interim, the patient remained asymptomatic until six days prior to admission where she had sudden onset of highgrade fever (highest temperature of 38.7C) with no other reported symptoms. Paracetamol was given with partial relief of symptoms.

Four days prior to admission, persistence of fever associated with abdominal pain and 3-4 episodes of loose stools hence consult was done. Urinalysis result showed urinary tract infection. Patient was sent home and started on cefixime.

Two days prior to admission, persistence of fever and loose stools with erythematous rash appearing over the periumbilical area, hands and feet. (Figure 1 and 2)

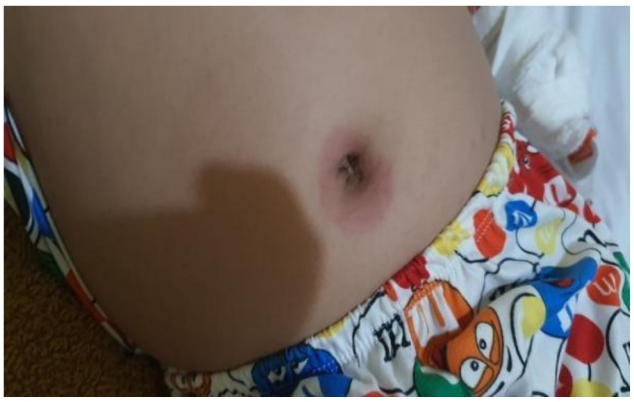


Figure 1. Erythematous rash noted at periumbilical area

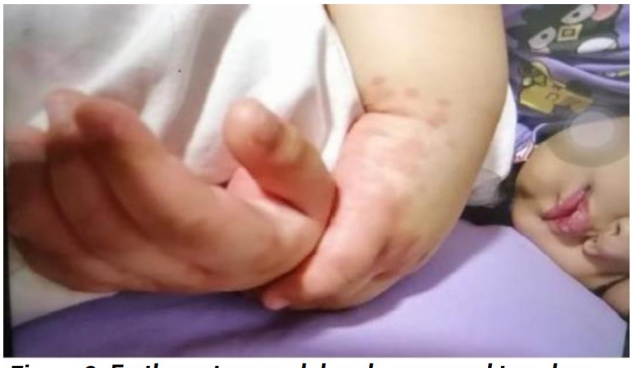


Figure 2. Erythematous rash hands appeared two days before admission

One day prior to admission, persistence of fever accompanied by reddish eyes with non-purulent discharge and severe abdominal pain prompted consult and was subsequently admitted.

On admission, the patient was irritable, febrile with conjunctival erythema, reddish dry lips, no strawberry tongue, no palpable cervical lymphadenopathy, slightly distended abdomen with normoactive bowel sounds, nontender, erythematous rash over umbilicus, feet and hands, minimal edema of hands and feet (Figure 3 and 4). The patient was referred to pediatric rheumatology with an assessment of probable COVID-19 multisystem inflammatory syndrome in children. Laboratory results showed elevated inflammatory markers (ESR and CRP) as well as leukocytosis with neutrophilia and lymphopenia on complete blood count (Appendix A,B). The patient's SARS COV 2 antibody test showed a positive IgG result (Appendix J).

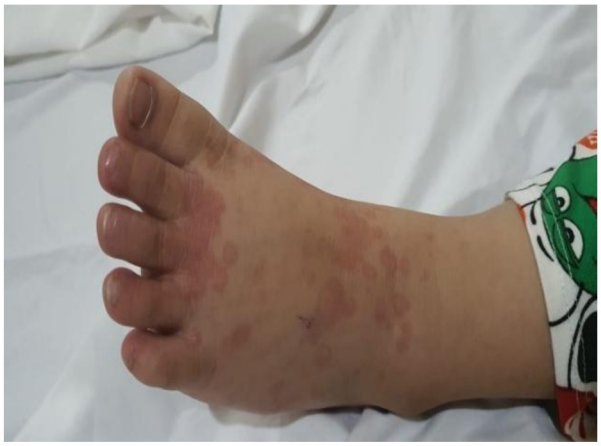


Figure 3. Erythematous rash now prominently seen over feet with noted minimal edema

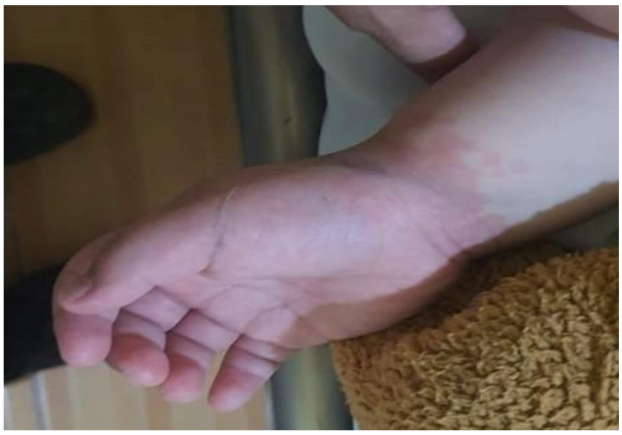


Figure4. Progression of erythematous rash on hands accompanied by minimal edema

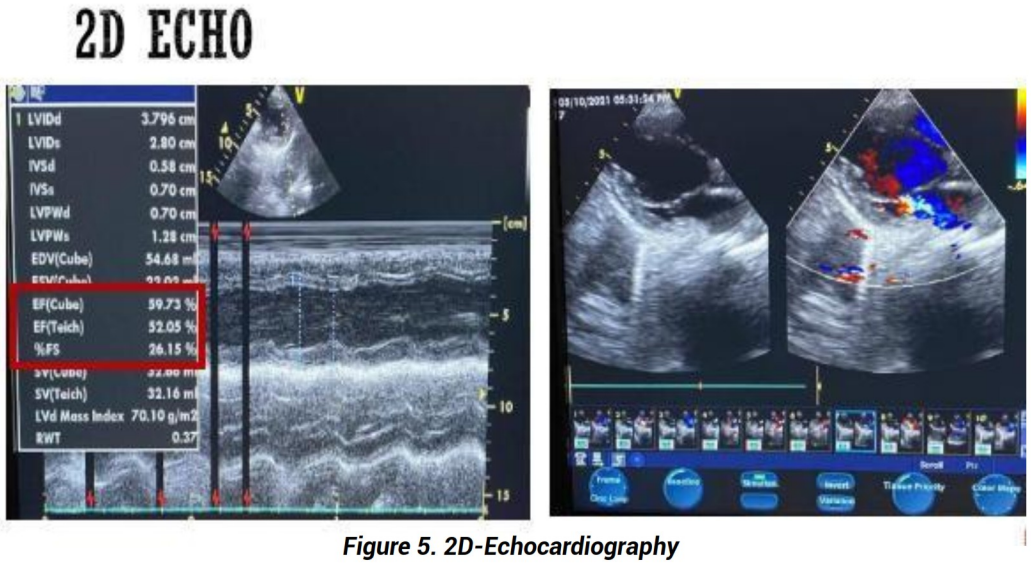


Figure 5. 2D-Echocardiography

On the second hospital day, the patient was hypotensive (BP of 80/60mmHg). She was transferred to Pediatric intensive care unit (PICU). Dopamine was shifted to norepinephrine and dobutamine. Intravenous immunogobulin was given at 2g/kg, prednisone and aspirin were continued.

On third hospital day, after IVIg infusion, the patient was stable with no recurrence of fever and abdominal pain. Inotropes were gradually tapered and norepinephrine was eventually discontinued. Blood and urine culture and sensitivity were unremarkable (Appendix G). The patient was transferred to a regular ward.

On fifth hospital day, repeat 2D Echo showed improved left ventricular function and decrease in right coronary artery dilation. Dobutamine drip was discontinued. She was discharged stable and improved on 7th hospital day. Take home medications were digoxin, aspirin and prednisone (tapering).

Differential Diagnosis

	Rule In	Rule Out
1. Kawasaki Disease	Fever Conjunctival erythema Erythematous rash on hands and feet	Gastrointestinal Symptoms Shock More Elevated Inflammatory markers
2. Toxic Shock Syndrome	Fever Erytematous Multisystem involvement Hypotension	Positive Blood cultures Positive for Serologic tests
3. Bacterial Sepsis	Fever Shock Elevated Inflammatory markers	Blood culture and Sensitivity: No growth Urine Culture and Sensitivity: no growth

DISCUSSION

Multisystem inflammatory syndrome in children (MIS-C) is a condition where body parts can become inflamed, including the heart, lungs, kidneys, brain, skin, eyes, or gastrointestinal organs (1). It is diagnosed clinically based on signs and symptoms presented by the patient persistent fever and dysfunction of one or more organs, such as the heart or gastrointestinal system, together with laboratory examinations to look for signs of inflammation in the body. Testing is also done to rule out other possible causes of the symptoms, such as other infections (2).

MIS-C patients had a male to female ratio of 1.37 to 1. Majority of patients had symptoms appearing around 4-6 weeks after COVID 19 infection. Hispanic and African MIS- C were commonly affected than non-Hispanic and Asians. Hispanic patients had more severe disease outcomes.

Table 1 shows the preliminary case definition of CDC and WHO.

Table 1

CDC case definition (ALL 4 CRITERIA MUST BE MET)	WHO case definition (ALL 6 CRITERIA MUST BE MET)
1. Age<21 years	1. Age 0 to 19 years
2. Clinical presentation consistent with MIS-C, including ALL of the following: a. Fever	2. Fever for >3 days
b. Laboratory evidence of inflammation Including but not limited to any of the following: • ↑CRP •↑ESR •↑Fibrinogen •↑procalcitonin •↑D-dimer •↑ferritin •↑LDH •↑IL-6 level •Neutrophilia •Lymphocytopenia •Hypoalbuminemia	3. Clinical signs of multisystem involvement (at least 2 of the following) •Rash, bilateral nonpurulent conjunctivitis or mucocutaneous inflammation signs(oral hands or feet) •Cardiac dysfunction, pericarditis, valvulitis or coronary abnormalities •Hypotension or shock •Evidence of coagulopathy •Acute gastrointerstinal symptoms (diarrhea, vomiting or abdominal pain)
c. Multisystem involvement 2 or more organ systems involved	4. Elevated markers of inflammation (eg, ESR, CRP or procalcitonin
d. Severe illness requiring hospitalization	
3. No alternative plausible diagnoses	5. No other obvious microbial cause of inflammation
4. Recent or current SARS-CoV 2 infection or exposure	6. Evidence of SARS-CoV 2 infection

Our patient is a 3 year old female who had intermittent high grade fever, with more than 2 multisystem involvement, all inflammatory markers were elevated. CDC included D-dimer, ferritin, lactate dehydrogenase. Both required that infections and other causes must have been ruled out and both required evidence of a recent or current sars cov 2 infection or exposure. Our patient's case satisfied both CDC and WHO case definition for MIS-C.

Our patient was noted to have overlapping signs and symptoms of (KD). However, clinical features of our patient that differed from KD are the following: 1. Abdominal pain; 2. Diarrhea; 3. Abnormal cardiac enzymes; 4. Immediate improvement of cardiac function after single IVIg treatment; 5. Higher inflammatory markers than patients with KD; 5. Previously diagnosed with COVID-19 or has exposure to patients positive to COVID-19.

Table 2 shows the difference between MIS-C and KD.

Table 2

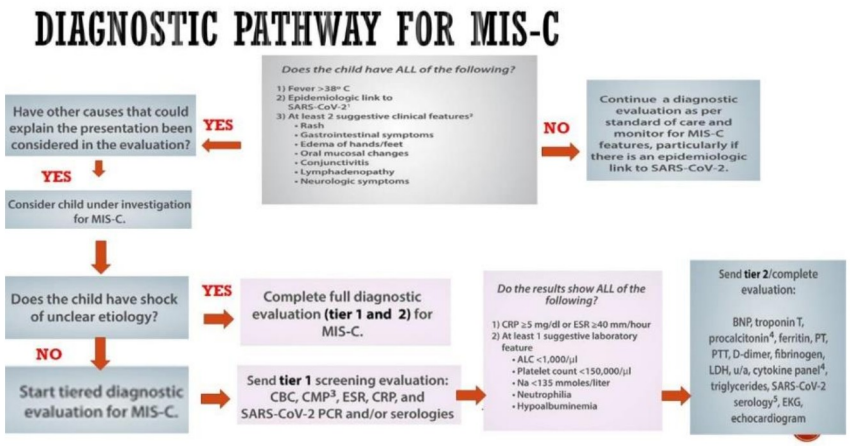
MIS-C	KAWASAKI DISEASE
Affects older children and adolescents	Typically affects infants and young children
Black and Hispanic children	Higher incidence in East Asia and children of Asian descent
Gastrointestinal symptoms are very common	Less prominent in classic KD
Myocardial dysfunction and shock occur more commonly	Less common with classic KD
More ELEVATED inflammatory markers	Elevated inflammatory markers
Absolute lymphocyte and platelet counts tend to be lower	Thrombocytosis

Whittaker, E, Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV2. JAMA, 2020;324(3):259-269

Different signs and symptoms related to MIS-C are not specific, however, diagnosis should be based on high index of suspicion and clinical judgment, taking into account the patient's history, severity of organ dysfunction and strongly elevated inflammatory markers.

Table 3 shows Diagnostic Pathway for MIS-C according to American College of Rheumatology

Table 3



Treatment goals of MIS-C are to stabilize patient with life threatening manifestations such as shock and to prevent long-term sequelae which may include coronary artery aneurysm, myocardial fibrosis/scarring, and fixed cardiac conduction abnormalities (4). Children diagnosed with MIS-C need close observation. Patients need to be admitted to the hospital, and some may need intensive care. Pediatric specialists in rheumatology, critical care, and cardiology can anticipate and address different aspects of the illness. Treatments include IV immunoglobulin (used to treat Kawasaki disease), and anti-inflammatory drugs (corticosteroids, and drugs blocking IL-1 or IL-6). Anakinra, an Interleukin 6 antagonist receptor may be considered for treatment of refractory to IVIg and glucocorticoids or in patients with contraindications to these treatments. Our patient was started on prednisone and aspirin when inflammatory marker results were elevated. Low-dose aspirin was used to decrease the risk of blood clots. Captopril, furosemide and digoxin was started when 2D Echo result showed left ventricular dysfunction, right coronary dilation, mitral regurgitation and pericardial effusion. Other treatments may be used depending on the results of laboratory tests.

SUMMARY

I have reported a case of Multisystem Inflammatory Syndrome in a 3-year-old female who presented with a 6 days history of fever. The incidence is uncertain, cases usually peak several weeks after being positive to COVID-19 or exposed to a confirmed patient. Prompt recognition of this syndrome enables clinicians to obtain proper diagnosis, treatment, and provide families with accurate prognostic information.

REFERENCES

1. COVID-19: Multisystem Inflammatory Syndrome in Children (MIS-C) clinical features, evaluation, and diagosis-UptoDate. https://www.uptodate.com/contents/covid-19-Multisystem inflammatory-syndrome-in-children-mis-c-clinical-features-evaluation-and diagnosisH4291751271
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Appendix A

CBC	05/09	05/13
WBC	25.0	**16.3**
N	0.91	**0.82**
L	0.06	**0.15**
M	0.03	**0.03**
RBC	3.89	**3.45**
Hgb	108	**97**
Hct	0.31	**0.28**
MCV	78.4	**80.9**
MCH	27.8	**28.1**
MCHC	35.4	**43.8**
Platelet	**356**	**618**

Appendix B

	05/09	05/13
ESR	75mm	
CRP	20.71	**99.67**
Procalcitonin	9.58ng/mL	
Serum LDH	335	**289**
AST	48	
ALT	36	
Creatinine	0.6 mg//dL	
Serum Albumin	**3.3g/dL**	

Appendix C

	05/10	05/13
BNP	>4130 (H)	
Fibrinogen	8.34g/L H	
Serum Ferritin	275.89 H	
D dimer	2345.02ng/mL H	**2003.28**
Troponin I	0.47 ng/mL H	**0.09**
Triglyceride		**158**

Appendix D

SERUM ELECTROLYTES (05/09)		
Na	130	**136 - 149**
K	3.4	**3.8 – 5.0**
Ca	**7.8**	**8.4 – 10.2**

Appendix E

05/09/2021	05/09/2021
CHEST XRAY: Reticular opacities seen in the right inner to mid lung zones, Pneumonia	Whole abdominal ultrasound: Enlarged liver with fatty changes, splenomegaly, enlarged but morphologically unremarkable kidneys

Appendix F

05/09/2021	05/09/2021
- Fair left ventricular systolic function at 52% to 54% - RCA dilation o Proximal 0.24cm to 0.36cm o Middle 0.22 to 0.35 o Distal 0.19 to 0.33cm - Pericardial effusion 0.47 to 0.75cm, RV side - No vegetation	- Good LV function 66% - MR trivial - + pericardial effusion 0.44 to 0.64cm, RV side - RCA dimensions: o Proximal 0.19 to 0.31 o Middle 0.21 to 0.34 o Distal 0.18 – 0.32

Appendix G

05/10 Blood Culture and sensitivity – No Growth	Urine Culture and Sensitivity – no Growth

Appendix H

	05/09	05/13
APTT	64.8 H	**28.9**
PT	13.4	**14.0**
Control	12.9	**12.9**
% activity	91.5%	**82.1%**
INR	**1.04**	**1.08**

Appendix I

5/11/ Urinalysis

Yellow, slightly turbid

Glucose: Negative Protein: Negative

pH 6.0 Specific Gravity: 1.010

RBC: 1-3 Pus cells: 6-8

Bacteria: Few

Appendix J

05/10/2021

RT PCR – Negative
COVID Antibody TEST:
IgM: negative
IgG : positive

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