Revisiting MIS-C: Extending the Exclusions

Following coronavirus disease 2019 (COVID-19) or asymptomatic severe acute respiratory system corornavirus 2 (SARS-CoV-2) infection, multisystem inflammatory syndrome following COVID-19 in children (MIS-C), is a relatively new entity with diagnosis based on preliminary case definition criteria, formulated to assist management of this potential life-threatening condition [1]. In the absence of standardized guidelines, there is a possibility of not only missing milder cases but also over diagnosing diseases with overlapping presentations, as MIS-C.

We report 11 children, initially treated as MIS-C, who got a different final diagnosis. Out of them four were diagnosed at our center and seven were referred from outside after MIS-C treatment. **Table I** illustrates the clinical and laboratory profile of these patients. Ten (91%) patients met the World Health Organization (WHO) case definition criteria at initial presentation. One referred patient was treated as MIS-C without meeting the criteria. Median age and male:female ratio were 8 (2-15) years and 1:2.66, respectively. Median time to arrive at final diagnosis was 2 (1-5) months. All had fever and raised inflammatory markers on re-admission.

The definitive diagnosis were hematolymphoid diseases in 4 (36%), collagen vascular diseases in 4 (36%), and infections in 2 (18%) children. One child had an inflammatory myo-fibroblastic tumor. Hematolymphoid diseases were diagnosed on bone marrow and tissue examination. Diagnosis of collagen vascular diseases was as per standard rheumatological guidelines and serological reports. Imaging aided diagnosis of inflammatory myo-fibroblastic tumor, Takayasu arteritis, Hodgkin lymphoma and lymphoproliferative disorder.

During initial admission, all received antibiotics and steroids. 18% (*n*=2) received IVIg and steroids, and 36 % (*n*=4) patients needed PICU care during their treatment. Five patients (45%) were discharged on aspirin. After definitive diagnosis, nine patients (82%) responded to the specific treatment, but two patients (18%) succumbed to their illness (Hodgkin lymphoma stage 4 and lymphoproliferative disorder). The collagen vascular disease group had high serum ferritin level [median (IQR) 1909 (1208) ng/mL]; whereas, hematolymphoid group had low neutrophil: lymphocyte ratio of 2.2 and low platelet count.

Case definition criteria for MIS-C were intentionally kept wide enough to include all possible cases and were open for revision with availability of more information. Broad, et al. [2] reported that 70 patients were diagnosed as MIS-C by pediatric multi-disciplinary team based on clinical features and evidence of inflammation. After investigations, treatment was discontinued in 13 (18.5%) patients as alternative diagnosis became available. Finally, only 57 (81%) patients were truly confirmed as MIS-C [2]. They did not report any significant difference in clinical and biochemical parameters between those who met and did not meet the diagnostic criteria in this study [2].

WHO mentions 'absence of other causes of inflammation' as one of the essential case-defining criteria but has emphasized upon infections as main mimicker of MIS-C. However; our cohort had mainly hematolymphoid and collagen vascular diseases masquerading as MIS-C. Recently, American College of Rheumatology guidelines recommend ruling out malignancy and autoimmune disorders before making a diagnosis of MIS-C [3].

Inflammation being a known hallmark in collagen vascular diseases, the criteria for case definition of MIS-C are met by many children with these disorders [4]. We observed that the median serum ferritin (1208 ng/mL) of these patients were higher than that of MIS-C patients at presentation [5]. Hematolymphoid diseases may be associated with secondary hemophagocytic-lymphohistiocytosis (HLH), which has inflammatory features similar to MIS-C [6]. However, the neutrophil to lymphocyte ratio in these patients was lower than that in MIS-C patients, and platelet count was less than 1 lakh in the majority (*n*=3, 75%) [5].

At the peak of the COVID pandemic, steroids were utilized extensively as a life-saving measure to treat MIS-C. However, two patients with hematolymphoid malignancies in our cohort succumbed, as steroids induced partial remission leading to delayed diagnosis and initiation of specific treatment. Additionally, positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV 2) antibody titers led to bias in diagnosing MIS-C. At our institute, out of 87 patients treated as MIS-C, 4 (4.6%) had different final diagnosis on follow up viz., collagen vascular disease (2 patients) and CVID with septic shock and Hodgkin lymphoma stage 4 (1 each) (Unpublished data). However, this should not discourage timely diagnosis and treatment of MIS-C, a life threatening condition.

Collagen vascular disorders, hematolymphoid diseases and atypical infections can initially present as MIS-C, and meticulous evaluation to rule out these is needed. Patients diagnosed and treated as MIS-C need to be followed-up to ensure absence of an alternate diagnosis and complete relief of symptoms.

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Table I Clinical and Laboratory Profile of Children Misdiagnosed as MIS-C

Age/ sex	*Initial presentation*[a]	*D-dimer (µg/mL)*	*ESR (mm/h)*	*CRP (mg/L)*	*Ferritin (ng/mL)*	*Re-admission*[b]	*Final diagnosis*	*Time to diagnosis (mo)*
Hematolymphoid								
6y/F	Cheilosis, abdominal pain	587	28	42	37	Inguinal lympha deno-pathy, abdominal pain	Acute leukemia	5 m
4y/F	Hypotension, pulmonary bleeding, regurgitation, abdominal pain,	5000	58	26	58	Ascites, pleural effusion	Lympho-proliferative disorder	1m
15y/M	Red tongue, oral ulcers, abdominal pain	2626	80	160	600	Jaundice splenomegaly	Hodgkins lymphoma stage 4	5 m
14y/M	Lower limb edema, rash, abdominal pain, vomiting	Not done	24	14	176	Pancytopenia	Aplastic anemia	1 m
Collagen vascular disease								
13y/F	Skin rash, ankle pain	11770	61	160	11326	Cervical lympha-denopathy, ankle and knee joint arthritis	SOJIA	3 m
14y/F	Abdominal pain, hypotension	319	70	85	445	Abdominal pain, feeble pulses	Takayasus arteritis	1 m
8y/F	Rash, Hypotension, abdominal pain, vomiting	1001	60	72	62	Cervical dystonia, lymphadenopathy, rash, wrist synovitis	Undifferentiated connective tissue disorder	5 m
9y/F	Rash, lower limb swelling, abdominal pain	2043	90	74	1971	Rash, arthritis	SOJIA	2 m
Infections								
2y/F	Rash, Hypotension, coronary dilatation, abdominal pain	10488	43	20	2550	Rash Shock	CVID septic shock	4m
2y/F	Red eyes, oral ulcer, abdominal pain	830	24	69	505	Abdominal pain	Brucellosis	1m
Other								
3y/M	Rash, conjunctivitis, dilated coronaries, abdominal pain	485	81	66	380	Abdominal pain, abdominal mass on USG	Inflammatory myofibroblastic tumor	1m

MIS-C: multisystem inflammatory syndrome following COVID-19 in children. ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; SOJIA: systemic onset juvenile rheumatoid arthritis; CVID: common variable immunodeficiency. [a]Along with fever >3 d; [b]along with fever and raised inflammatory markers.

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