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COVID-19 in Children: A Case Report of Multisystem Inflammatory Syndrome (MIS-C) in Tripoli-Libya

Case Report

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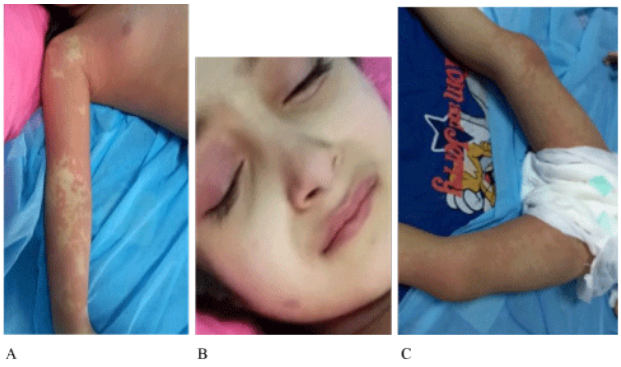
Case Report

As COVID-19 continues to spread in countries all over the world included Libya, the impact of the disease among children, initially considered less important [1], will increasingly be more relevant. The role of children in viral transmission and its impact in epidemic expansion, as well as the extent of the diversity of clinical presentation, are still unclear. At the end of April, the United Kingdom South Thames Retrieval Service alerted on a new clinical picture manifesting as a hyper-inflammatory syndrome, with multi-organ involvement similar to Kawasaki Disease and with potential evolution to a shock syndrome. This represented a new phenomenon affecting previously asymptomatic children with SARS-CoV-2 infection [2]. This Multisystem Inflammatory Syndrome in Children (MIS-C) associated with SARS-CoV-2 infection occurs weeks after infection and may evolve unnoticed.

Here in we report a case of SARS-CoV-2 related MIS-C observed at end of November 2020. A previously healthy 7-year-old female child was admitted to the paediatric intensive in care unit at Cartage Clinic with a five day history of high-grade fever, accompanied by headache, sore throat, abdominal pain (her abdomen was tender and rigid), skin rash Figure 1 (blanching erythematic rash over her lower limbs, trunk, then upper limbs), generalised fatigability, arthritis, bilateral non suppurative conjunctivitis, cracked lips and poor appetite. There was history of recent contact to one member of her family who had been in Turkey, all her family members were not tested a COVID-19 and all remained asymptomatic.



A B C

Figure 1: (a-b-c) erythematic skin rash all over the body, congestion of the lips and periorbital edema and erythema. Image shared with parental permission.

Figure 2: Non-suppurative conjunctivitis and peeling fingers. (After treatment).

Table 1: Laboratory Values throughout Hospitalization

	Reference Range	Patient Result time of admission	Patient Result during treatment	Patient Result pre discharge
WBC	4-15 103/µL	10.3	23	14.2
Hemoglobin	9-11g/dl	11.1	9.8	8.5
Platelet	150-450 10^3/µL	130	98	301
Random serum glucose	70-120 mg/dL	108	110	70
Creatinine	0.6-1.4 mg/dL	0.6	0.7	0.6
Urea	10-50 mg/dL	26	27.1	20
Na+	135-155 mmol/L	136.2	136.1	136
K+	3.5-5.5 mmol/L	4.01	2.89	3.91
CL-	98-107 mmol/L	101.2	105.8	103.4
LDH	100-190 units/L	218		
Total serum bilirubin	0.2-1.2 mg/dL	0.5	0.6	
Direct bilirubin	0.0-0.2 mg/dL	0.12	0.13	
Albumin	3.2–5.2 gr/dL		2.9	
AST	Up to 32 units/L	9	10	
ALT	Up to 32 units/L	13	7	
Alkaline phosphatase	Up to 747 units/L	156	139	
S.cholesterol	<200 mg/dL		127	
S.triglycerides	<150 mg/dL		289	
L.D.L	0-130 mg/dL		61	
H.D.L	35-60 mg/dL		8	
S.IRON	50-120 ug/dL		42	
CK-MB	Up to 25 U/L	249	6	
TROPONIN-I	Up to 0.30 ng/mL		0.6	
PT	11.0-13.5 seconds		15.9	
PTT	30-40 seconds		34	
INR	0.84–1.14		1.29	
D-dimer	0–500 ng/mL	3920	6540	740
ESR	0.0-29 mm/hour	81	103	
CRP	0-0.5mg/dL	173.28	182.05	12.21
Ferritin	11–205 ng/mL	1537	824	252.3
Fibrinogen	200–500 mg/dL		300	
C3	86–186 mg/dL	88.47	100	
C4	16–47 mg/dL	34.22	28	
IL-6	0–7 pg/mL	Not available		
ANA titer	0.8-1.2		negative	
P ANCA	Negative < 12		<3	
C ANCA	Negative < 12		6.8	
Anti ds DNA IGG	< 20		4.5	
Anti ds DNA IGM	<20		21.40	
CMV IgM	Negative below 0.9	0.187		
EBV IgG	Positive above 25 u/ml	>400		
HSV IgM	Negative below 0.9	0.300		
Blood and Urine Culture	No growth	No growth		

Abbreviations: WBC: White Blood Cells; CRP: C-Reactive Protein; IL-6: Interleukin-6; INR: International Normalized Ratio; IV: Intravenous. LDH; Lactate Dehydrogenase; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; PT: Prothrombin time; PTT: Partial Thromboplastin Time; INR: International Normalized Ratio; ESR: Erythrocyte Sedimentation Rate

Table 2: Preliminary case definitions for MIS-C

	MIS-C associated with COVID-19	PIMS-TS	MIS-C associated with COVID-19	Complete Kawasaki disease	Incomplete Kawasaki disease	Kawasaki disease shock syndrome
Organisation or publication	WHO[6]	Royal College of Pediatrics and Child Health[39]	US Centers for Disease Control and Prevention[37]	American Heart Association[40]	American Heart Association[40]	Kanegaye et al,[41]
age	0–19 years	Child (age not specified)	<21 years	Child (age not specified)	Child (age not specified)	Child (age not specified)
Inflammation	Fever and elevated inflammatory markers for 3 days or more	Fever and elevated inflammatory markers	Fever and elevated inflammatory markers	Fever lasting 5 days or more*	Fever lasting 5 days or more*	Fever
Main features	Two of the following: (A) rash or bilateral non-purulent conjunctivitis or mucocutaneous inflammation signs (oral, hands, or feet); (B) hypotension or shock; (C) features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiogram findings or elevated troponin or N-terminal pro B-type natriuretic peptide); (D) evidence of coagulopathy (elevated prothrombin time, partial thromboplastin time, and elevated D-dimers); and (E) acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pa	Single or multiple organ dysfunction (shock or respiratory, renal, gastrointestinal, or neurological disorder; additional features (appendix 6 pp 3–4)	Clinically severe illness requiring hospitalisation; and multisystem (two or more) organ involvement (cardiac, renal, respiratory, haematological, gastrointestinal, dermatological, or neurological)	Four or more principal clinical features: (A) erythema and cracking of lips, strawberry tongue or oral and pharyngeal mucosa; (B) bilateral bulbar conjunctival injection without exudate; (C) rash; (D) erythema and oedema of the hands and feet in acute phase and periungual desquamation in subacute phase; and (E) cervical lymphadenopathy	Two or three principal clinical features or a positive echocardiogram	Kawasaki disease-like clinical features and any of the following causing initiation of volume expansion, vasoactive agents, or transfer to the intensive care unit: systolic hypotension based on age, or a decrease in systolic blood pressure from baseline by 20% or more, or clinical signs of poor perfusion
Exclusion	Other microbial cause of inflammation	Any other microbial cause	Other plausible alternative diagnoses			Other microbial cause

SARS-CoV-2 status	Positive RT-PCR, antigen test, or serology; or any contact with patients with COVID-19	RT-PCR positive or negative	Positive RT-PCR, serology, or antigen test; or COVID-19 exposure within the past 4 weeks before symptom onset			

Abbreviations: MIS-C: Multisystem Inflammatory Syndrome in Children; PIMS-TS: Paediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2; SARS-CoV-2: Severe acute respiratory syndrome corona virus 2

Table 3: Differential diagnosis of MIS-C

	MIS-C	KD	TSS	HLH/MAS
Dominantly affected age group	School-age children and adolescents	Infants and toddlers	Any age	Any age
Prolonged fever	Yes	Yes	Yes	Yes
Fissured lips	Common	Typical	Possible	Insufficient data
Nonexudative conjunctivitis	Common	Typical	Possible	Possible
Hypotension	Common	Possible	Typical	Possible
GIS symptoms	Very common	Rare	Common	Rare
Coronary aneurysms	Possible	Common	Insufficient data I	Insufficient data I
Heart failure	Common	Possible	Rare	Rare
Neutrophilia	Yes	Yes	Yes	No
Lymphopenia	Yes	No	No	Yes
Thrombocytopenia	Yes	No	Yes	Yes
CRP	Elevated	Elevated	Elevated	Elevated
Ferritin	Elevated	Normal, or elevated	Normal	Elevated
Hypertriglyceridemia	Common	No	No	Typical

CRP: C-Reactive Protein; GIS: Gastrointestinal System; HLH/MAS: Hemophagocytic Lymphohistiocytosis/ Macrophage Activation Syndrome; KD: Kawasaki Disease; MIS-C: Multisystem Inflammatory Syndrome in Children; TSS: Toxic Shock Syndrome

On physical examination, she was febrile had high fever (40°C), tachypnic (50 C/min), tachycardic (130 b/min), hypotensive (50/30 mmHg) with delayed capillary refill time (4 second), lethargic, her oxygen saturation was 95-97%, she was semiconscious, GCS = 13, non suppurative conjunctival erythema, strawberry tongue, non blanching maculaopapular skin rash all over her body, she has sign of meningeal irritation (neck stiffness and brudzinski sign).

Laboratory tests showed anemia (haemoglobin of 10.5 mg/L and hematocrit of 30.3%), 18 leukocytes/ mm^3 (91% polymorphonuclear) but with only (9%) lymphocytes/mm^3. Hypoxemia, with a saturation of 93.5% with arterial blood gas of pO2 of 63 mmHg and pCO2 of 29 mmHg, bicarbonate of 20 mmol/L, BE: −2.3 mmol/L, were documented along with a chest tomography which showing left side heterogeneous opacity, abdominal ultrasound show splenomegaly with mild to moderate ascites, The electrocardiogram and echocardiography was normal, MRI brain normal, lumber puncture was normal.

On the third day of hospitalization, the patient showed high levels of inflammatory markers, including and a C-reactive protein (CRP) of 182 mg/L and d-dimer of 6540 ng/mL associated high ferritin (1537 ng/mL and hypoalbuminemia (2.9 g/dL), high Cardiac enzymes including Creatine kinase (CK-MB) 249 U/L Troponin I 0.6 ng / mL, prolonged coagulation profile PT, INR, with normal lactic acid, Creatinine, AST, ALT with no sign of any renal involvement as the renal function test remain normal in all days of hospitalization , results of blood , urine and cerebral spinal fluid cultures results negative and also our laboratory tests results negative for EBV, CMV, HSV, Rickettsia, Infectious Mononucleosis.

Nasopharyngeal swabs at admission and on the 8th day of hospitalization, processed at the service reference laboratory detected SARS CoV-2. On the 6th day of hospitalization d-dimer levels were higher (5000ng/mL) with CRP of 182 mg/L. Autoantibodies tests were negative (anti-neutrophil cytoplasm — ANCA, anti-cardiolipin IgM and anti-SM antibodies) as was the serology to HIV and Hepatitis B/C

Given that MIS-C is a rare but life-threatening multisystem condition, there is an urgent need to plan available treatment options. However, our goal at the beginning is to stabilize patient vital signs, as patient has poor perfusion and hypotension, we started dopamine iv infusion, 20 ml / kg intravenous (IV) state of normal saline and paracetamol IV infusion has be given.

Antibiotic administration cannot be delayed due to the possibility of toxic shock syndrome. It is also important to highlight the team's mandatory use of personal protective equipment from the start of treatment.

the patient received vancomycin, ceftazidime and clarithrmycin for 10 days concomitantly with intravenous immunoglobulin IVIG 2g\kg\day in 1st day of admission, after 3 days she received methylprednisolone bolus started with 30mg / kg /dose for 2 days due to slow progression and signs of macrophage aggravating syndrome (MAS) then continue with 1 mg\kg\dose twice per day and then started tapering, with D-dimer 6540ng\ml, Enoxaprin subcutaneous injections (SC) 1mg/kg were used twice daily, the D-dimer level started to decline 6 days following IV immunoglobulin treatment to reach 740 ng/mL, the level of albumin was 2.9 g/dL so we give human albumin 20grams, Lowest platelet count was 98 103/μL 1 day after IV immunoglobulin treatment, and return to normal on 6th day of treatment, ferritin level reach 1537 ng/mL and started to decline 4 days following IV methylprednisolone treatment to reach 252 ng/mL

Peak CRP of 182 ng/mL and WBC of 23 103/μL started to decline 10 days following IV antibiotic combination treatment.

Clinically patient start to show improvement on the 6th day, her skin rash disappeared, her fever subsided and blood pressure return to normal,

The patient stay in pediatric intensive care unit (ICU) for 7 days and then transferred to pediatric isolation rooms to stay for 5 days, before discharged most of laboratory results returned to normal, abdominal ultrasound and echocardiography was both repeated and there results were normal, C-reactive protein (CRP) of 12 mg/L and d-dimer of 740 ng/mL, ferritin (252 ng/mL and serum albumin (3.2 g/dL), her coagulation profile PT, INR return to normal, then patient discharged on Enoxaprin SC 0.5mg/kg for one week, tapering of methylprednisolone tablet, and follow up 3 weeks after discharged

In spite of only supportive measures, the child evolved with resolution of ascites, normalization of laboratory tests, being discharged on the 12th day of hospitalization and was asymptomatic.

At the time of diagnosis, this was one of the first MIS-C cases in Libya. Fever and abdominal pain are common manifestations of the syndrome [3] that usually present also with hypotension and cardiac dysfunction [6] that were not outstanding in this child. However, multi-organ involvement, the confirmed SARS-CoV-2 serological tests and laboratory alterations including lymphopenia and inflammatory markers, hallmarks of the syndrome, support the diagnosis, that fulfil the CDC, BMH and WHO criteria for MIS-C [3,5,13]. The case definition of MIS-C is extremely broad and may not be specific enough [6] but is useful and may be improved as more information is obtained. As the virus spreads, the presence of antibodies to the virus will become more prevalent, and documenting past COVID-19 infection with serology may not be so helpful, but today this is the only indication for the clinical use of a serological test [7,12]. Thus, although serologic testing help establish a diagnosis when patient present with late complications of COVID-19 illness, such as MIS-C, both clinical and laboratory criteria need to be improved.

The lack of viral RNA detection is not impediment for the diagnosis [3,5], as the syndrome may occur after viral clearance from upper airways and false negative results are not uncommon. Antibodies appear 1–2 weeks after infection. In primary infections, IgM responses typically develops first, eventually waning and with IgG response dominating thereafter. Thus, high levels of IgG in the absence of IgM may suggest a time of weeks or even months from infection [7]. However, different kinetics of antibody appearance has been described in COVID-19 cases, with atypical antibodies kinetics, and a longer persistence of IgM may occur [8].

Age and clinical features are characteristic of the initial descriptions of MIS-C in the literature, while fever, shock,

abdominal pain, vomiting and diarrhea are common presenting features [9]. Kawasaki Disease (KD) shares some common features with MIS-C, but Asian children have the highest incidence KD6 whereas MIS-C seems rare in this population [1,6]. Moreover, KD occurs mostly in children less than five years of age, with a peak incidence at 10 month of age [6]. In a prospective observational study with 21 children and adolescents admitted with features of Kawasaki-like disease over a 15-day period, during the COVID-19 pandemic in Paris, France, 12 (57%) had African ancestry [10].

*In the presence of four or more principal clinical features, particularly when redness and swelling of the hands and feet are present, the diagnosis of Kawasaki disease can be made with only 4 days of fever.

This child recovered with only supportive care, no longer requiring intensive care after a few days and showing complete recovery. Although a severe illness, with 68% requiring intensive care [4], few deaths have been reported in other countries, often resulting from complications related to therapeutic intervention [6]. This is an important point to be observed when exploratory therapy is considered. Children have been treated with anti-inflammatory treatment, including parenteral immunoglobulin and steroids [3,11] and a few received TNF-Alfa inhibitors, IL-1 and Il-6 receptor antagonists [3]. However, a better understanding of the pathogenic mechanism of the disease may help defining the appropriate interventions for specific cases. Although some authors have described MIS-C as a type of cytokine storm, important differences from the prototype antibody chimeric reactions, observed with some monoclonal therapeutic agents, have been highlighted, 11 and different immunopathogenic mechanisms may be expected. Moreover, high serum IL-6 is also common in some systemic juvenile arthritis6 and the role of cytokines and other features of MIS-C still lack proper understanding to guide therapy. There is also an urgent need to standardize data describing clinical presentations, severity, outcomes and epidemiology [13].

Clinical features suggestive of this syndrome should prompt alertness among primary care, emergency units and paediatricians during the expected expansion of COVID-19 in Libya and in other countries.

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