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Original Article

First Tunisian Cluster Admissions of Critically Ill Patients with Multisystem Inflammatory Syndrome in Children (MIS-C)

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Competing interests: The authors declare no conflict of Interest.

Abstract. ***Background:*** **Multisystem inflammatory syndrome in children (MIS-C) is a new emerging severe disease that is temporally related to previous exposure to coronavirus infection disease (COVID-19).**
Aim: **To describe the clinical features, laboratory findings, therapies, and outcomes for the first Tunisian cluster admissions of critically ill children with severe MIS-C.**
Methods: **Retrospective study conducted from November 01 to November 30, 2020**
According to the WHO definition case, we included eight children aged less than 15 years who were admitted to our pediatric intensive care and met MIS-C criteria. We reviewed all patients' medical records to collect demographic and clinical data, severity scores, laboratory test results, echocardiographic findings, treatment, and outcomes.
Results: **The median age was 8 years (IQR: 4-10years). All children were previously fit and well. Seven patients were boys. Known exposure to COVID-19 was reported in 4 cases. Fever and gastrointestinal symptoms were reported in all cases. Five patients had marked abdominal pain and were examined by the surgeon for possible appendicitis. Seven patients had diarrhea. On examination, we found rash (n=7), conjunctivitis (n=7), cheilitis (n=5), and meningism (n=3). We reported cardiac dysfunction in 7 cases and shock with hypotension in 3 cases. All patients received immunoglobulins, methylprednisolone, and a low dose of aspirin. No deaths occurred.**
Conclusion: **We reported here the first Tunisian cluster admissions of 8 critically ill children with MIS-C to highlight the increase of a new severe emerging disease with evidence of prior COVID-19 infection in older children.**

Keywords: Multisystem inflammatory syndrome; Children; Critical care.

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Introduction. Multisystem inflammatory syndrome in children (MIS-C) is a new emerging severe disease that is temporally related to previous exposure to coronavirus infection (COVID-19). It is characterized by fever, abdominal pain, gastrointestinal and cutaneous symptoms, and hemodynamic alterations. Since late April 2020, there has been an increasing number of worldwide reports of children with MIS-C.[1,2,3,4,5]

The world health organization (WHO) has developed a preliminary case definition for MIS-C in July 2020.[6] It

includes clinical presentation, elevated markers of inflammation, evidence of infection, or contact with patients who have COVID-19 after excluding other obvious microbial causes of inflammation.

We describe the clinical features, laboratory findings, therapies, and outcomes for the first cluster of 8 children with MIS-C admitted in a Tunisian pediatric intensive care unit (PICU). Informed consent has been obtained from patients and their parents.

On November 29, 2020, we alerted the Tunisian National Observatory of New and Emerging Diseases (ONIAM) about an abnormal increase of very ill children with cardiac dysfunction requiring intensive care admission.

Patients and Methods.

Setting. The study was conducted in the PICU of Children's hospital Bechir Hamza of Tunis. The PICU is a university-affiliated children's hospital. The PICU has 14 beds (650 admissions/year) and provided 2 beds for COVID-19 critically ill children. From March to September 2020, no admissions occurred with a diagnosis of COVID-19.

Study design. We conducted a retrospective study between November 1 and November 30, 2020. We included all children aged less than 15 years who were admitted to our PICU and met MIS-C criteria according to the WHO definition case.[6]

We reviewed the medical records of all patients to collect demographic and clinical data (comorbidities, symptoms, delay between symptom onset and PICU admission, organs involvement), severity scores (PRISM III), laboratory test results (markers of inflammation and cardiac enzymes), echocardiographic findings (left ventricular ejection fraction (LVEF)), treatment (medical treatment and need for mechanical ventilation or noninvasive ventilation), and outcomes (length of stay, mortality).

A clinical diagnosis of shock was established in the presence of arterial hypotension, the need for vasoactive therapy to maintain normal blood pressure, or the presence of signs of hypoperfusion despite adequate fluid resuscitation.[7] Hypotension was defined by systolic or diastolic blood pressure values below the 5th percentile of the reference values for height or less than 90/50 for children aged 10 years or older.[8] Acute cardiac dysfunction was defined as the appearance of reduced left ventricular ejection fraction (LVEF) less than 55%.[9] Renal involvement was defined as an increase in serum creatinine levels of double the standard limits for the patient's age according to pediatric pRIFLE.[10] Liver involvement was defined as an increase in transaminase or bilirubin levels twice above baseline or average values for the patient's age.

All patients were tested for SARS-CoV-2 (nasopharyngeal reverse transcription-polymerase chain reaction (QIASTAT- RP-SARS-COV-2) and had serologic tests (electrochemiluminescence immunoassay/Cobas e 411)

Results. In the study period, 35 patients aged less than 15 years were admitted to the PICU. Only three patients required intensive care admission for respiratory distress and confirmed COVID-19 infection.

We reported eight children admitted with MIS-C. Seven patients were boys. The median age was eight years (interquartile range IQR:4-10 years). All children were previously fit and well. No one had obesity. The first patient with confirmed MIS-C in our cohort was admitted on November 3, 2020. Known exposure to COVID-19 was reported in 4 cases. Demographic, clinical data, laboratory test findings, and echocardiographic findings were shown in **table 1**.

Table 1. Clinical Features of 8 Children with Multisystem Inflammatory Syndrome in Children.

	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**	**Patient 6**	**Patient 7**	**Patient 8**
Age in years	10	9	9	4	7	10	7	6
Sex	M	M	M	M	M	M	F	M
Comorbdity	0	0	0	0	0	0	0	0
Body mass index (kg/m^2)	20	16.5	18	18	14	25	20	17.4
Delay between symptom onset and PICU admission (days)	15	6	9	6	4	7	4	7
PRISM III	3	8	9	4	4	8	13	11
Presenting symptoms:								
Fever	+	+	+	+	+	+	+	+
Diarrhea	+	+	+	+	-	+	+	+
Abdominal pain	++	++	++	+	+	++	++	+
Vomiting	+	-	+	+	-	-	-	+
Headache	+	+	+	+	+	+	-	-
Sore throat	+	+	-	-	-	+	+	-

Myalgias	+	-	+	+	+	+	+	-
Rash	+	+	+	+	+	-	+	+
Conjunctivitis	+	+	+	+	-	-	+	-
Cheilitis	-	+	-	+	+	-	+	+
Lymphadenopathy	-	-	-	+	-	-	-	-
Respiratory distress	-	-	-	-	-	+	-	+
Hypotension	+	-	-	-	-	+	-	+
Acute cardiac dysfunction	+	+	+	-	+	+	+	+
Altered mental status	-	-	-	-	-	-	-	+
Meningism	-	-	+	-	+	+	-	-
Laboratory initial test findings								
C reactive protein (mg/L)	138	349	246	194	166	341	281	332
(Ref: 0.0–0.9 mg/L)								
Procalcitonin (ng/mL)	N/A	6.7	46	1.5	6.9	108	15.3	63
(Ref: 0.0–0.1 ng/mL)								
Leucocyte count (cells/µL)	23900	9900	12900	6900	3800	15800	5500	19800
(Ref: 6000–15000 cells/µL)								
Lymphocyte count (cells/µL)	1200	730	410	1540	600	1400	440	780
(Ref: 2000–6000 cells/µL)								
D-dimer (ng/ml)	4957	4500	7860	960	720	1640	1000	1410
(Ref: 0.0–500 ng/mL)								
Fibrinogen (g/L)	6.5	2.5	5.9	2.9	3.5	4	5.7	6
(Ref: 2–4 g/L)								
Ferritin (ng/mL)	1862	N/A	513	149	566	568	840	893
(Ref: 27–375 ng/mL (M)/ 12-135 ng/mL (F))								
Troponin (ng/L)	633	160	980	17.9	10.8	16367	36	377
(Ref: 0.0–16 ng/L)								
Brain type natriuretic peptid (pg/mL)	>25000	1039	>25000	5260	416	22500	3200	>25000
(Ref: 0.0–100 pg/mL)								
Lactate (mmol/L)	1.9	0.6	0.3	0.6	0.5	1.9	1.3	1.5
(Ref: < 2 mmol/mL)								
Natremia (mEq/L)	132	131	138	132	124	127	127	122
(Ref: 135–145 mEq/L)								
Acute kidney injury	-	-	+	-	-	+	+	+
LVEF (%)	34	40	30	60	44	12	38	11
Nasopharyngeal SARS-CoV-2 PCR	-	-	-	-	-	-	-	+
Serologic test of SARS-CoV-2	+	+	+	+	+	+	+	+
Known SARS-CoV-2 exposure	-	-	-	+	+	+	+	-

PICU, pediatric intensive care unit; LVSF, left ventricular systolic function; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; PCR, polymerase chain reaction.

Fever and gastrointestinal symptoms associated with pain were reported in all cases. The median delay between fever and PICU admission was 6.5 days (IQR: 4-15 days). Five patients had marked abdominal pain and were examined by the surgeon for possible appendicitis. Abdominal echography was performed in 3 cases, and an abdominal computed tomography scan in one case and showed mesenteric lymphadenitis in 2 cases and a peritoneal effusion pelvic fluid in 1 case. Seven patients had diarrhea. On examination, we found rash (n=7), conjunctivitis (n=7), cheilitis (n=5), and meningism (n=3). A lumbar puncture was performed in one case before admission in PICU for possible meningitis. We reported cardiac dysfunction in 7 cases and shock with hypotension in 3 cases. The LVEF was less than 30 % in 2 subjects who presented the most severe MIS-C form with higher inflammation markers (C-reactive protein, procalcitonin).

Laboratory test findings showed an increased level of C-reactive protein and procalcitonin in all cases without microbial cause. We reported lymphopenia, increased fibrinogen level, and D-dimer levels in all patients. Troponin and pro-brain natriuretic peptide (pro-BNP) levels were elevated in all cases presenting with cardiac dysfunction; however, the lactate level was normal. Four patients had an acute kidney injury. Two patients had an increase in lipase levels up to 3 times average.

All patients had positive SARS-COV-2 serology. Only one patient had a positive nasopharyngeal RT-PCR SARS-COV-2 testing, as shown in **table 1**.

Treatment and outcomes for our cohort were shown in **table 2**. All patients required respiratory support; three were mechanically ventilated and had severe cardiac dysfunction with hypotension. Echocardiographic measures improved under inotropic agents (dobutamine and milrinone). One patient required levosimendan. Complete recovery of left ventricular function was observed at a median delay of 4 days (IQR: 1-7 days) after admission. All patients received intravenous immunoglobulin (IVIG:1 dose of 2 grams per kilogram), methylprednisolone (10 milligrams per kilogram per day for three days), and a low dose of aspirin. Low-molecular-weight-heparin was administered in five patients. Antibiotics were used in two cases, but the treatment has been stopped on day 3. The median duration of fever was one day (IQR: 1-4 days). No abnormality in the coronary artery was found. No deaths occurred in our small cohort. All patients were discharged from PICU after a median length of stay of 5.5 days (IQR: 2-10 days). All children will be monitored into the future for the follow-up.

Discussion. To our knowledge, we reported the first cases of confirmed MIS-C in Tunisia and North Africa. On November 29, 2020, we alerted the Tunisian National Observatory of New and Emerging Diseases about an increase of very ill children admitted in our PICU with a diagnosis of MIS-C associated with SARS-COV-2. There were similar reports from other pediatric departments in Tunisia, but we did not yet have a national registry to collect data about all cases. In Africa, the first reports were published by South African authors. Web et al.[11] reported 23 cases of confirmed MIS-C.

The WHO, the Royal College of Pediatrics in the United Kingdom, and the US Centers for Disease Control and Prevention CDC established an MIS-C definition case.[12,13] Our eight patients fulfilled the criteria for the diagnosis of MIS-C. Symptoms of fever, abdominal pain, and cardiac dysfunction with elevated inflammation markers and elevated troponin and pro- BNP levels were the most seen features in MIS-C patients requiring intensive care. All patients except one had a cardiac dysfunction requiring inotropic agents. MIS-C can be observed without heart failure, but most patients admitted in intensive care units presented cardiac dysfunction or shock.[5,14,15,16] Grimaud et al.[17] reported the first case series of acute myocarditis with major systemic inflammation following SARS-COV-2

Table2. Support measures and pharmacological treatments administered to patients admitted for MIS-C.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Vasoactive support :								
Dobutamine	+	+	+	+	+	+	+	+
Milrinone	+	-	+	-	-	-	-	+
Levosimendan	-	-	-	-	-	+	-	-
Norepinephrine	-	-	-	-	-	+	-	+
Ventilation support								
MV / duration (days)	+ (3)	-	-	-	-	+(5)	-	+(5)
High flow nasal cannula	+	-	+	+	+	-	+	-
Neuromuscular blockade	-	-	-	-	-	+	-	+
Anti-inflammatory therapy								
Intravenous immunoglobulin (2g/Kg)(number of doses)	+ (1)	+ (1)	+ (1)	+ (1)	+ (1)	+ (1)	+ (1)	+ (1)
Methylprednisolone (10mg/kg/day); 3 days	+	+	+	+	+	+	+	+
Other therapies								
Anticoagulation	+	-	+	++	-	+	+	-
Antibiotics (duration in days)	+ (3)	-	-	-	-	+ (4)	-	-
Length of stay In PICU (days)	7	3	7	4	2	10	5	6

MV, mechanical ventilation; PICU, pediatric intensive care unit.

infection in twenty children. The cardiac function for our cluster admissions had been improved in a few days, and the prognosis was well for all. Dobutamine was the first agent used because of its selective inotropic effect. Three patients required milrinone, and one patient also required levosimendan. The same features were reported in the literature.[18,19] Avoiding fluid overload should be considered in all stages of the disease.

All our patients received IVIG with methylprednisolone. Most reported MIS-C were treated using the standard protocol for Kawasaki disease (KD), IV IG.[18,20,21] KD has been related to the occurrence of different viral infections in children, but that its direct, unequivocal cause is still unclear.[22] Evidence for IVIG and glucocorticoids in MIS-C is also based on their use in KD and fulminant myocarditis, two conditions that resemble MIS-C in some aspects.[23] There is no consensus for the treatment of severe MIS-C in our country. We choose to treat our critically ill patients with an association of IVIG and steroids. A patient with MIS-C is considered to have a refractory disease when the child has persistent fever and/or significant end-organ involvement despite initial immunomodulatory treatment. Anakinra had been used in some case series[15,17] and was recommended for the refractory disease.[23] This treatment was not easily available in our PICU. The small number of cases globally should conduct all intensivist pediatricians to coordinate for a multicenter study.

Conclusions. We reported the first Tunisian small cluster admissions of eight critically ill children in our PICU to highlight the increase of a new severe emerging disease with evidence of prior COVID-19 infection in older children. Additional epidemiologic data are needed to estimate the prevalence of MIS-C.

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