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Acute heart failure in multisystem inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2 pandemic

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Abstract

Background: Cardiac injury and myocarditis have been described in adults with COVID-19. SARS-CoV-2 infection in children is typically minimally symptomatic.
We report a series of febrile pediatric patients with acute heart failure potentially associated with SARS-CoV-2 infection and the multisystem inflammatory syndrome in children (MIS-C) as defined by the US Centers for Disease Control.
Methods: Over a two-month period contemporary with the SARS-CoV-2 pandemic in France and Switzerland, we retrospectively collected clinical, biological, therapeutic, and early outcomes data in children who were admitted to pediatric intensive care units in 14 centers for cardiogenic shock, left ventricular dysfunction and severe inflammatory state.
Results: Thirty-five children were identified and included in the study. Median age at admission was 10 years (range 2-16 years). Co-morbidities were present in 28% including asthma and overweight. Gastrointestinal symptoms were prominent. Left ventricular ejection fraction was <30% in one third; 80% required inotropic support with 28% treated with ECMO. Inflammation markers were suggestive of cytokine storm (interleukin 6 median 135 pg/mL) and macrophage activation (D-dimer median 5284 ng/mL). Mean brain natriuretic peptide was elevated (5743 pg/mL). Thirty-one/35 (88%) patients tested positive for SARS-CoV-2 infection by PCR of nasopharyngeal swab or serology. All patients received intravenous immune globulin, with adjunctive steroid therapy used in one third. Left ventricular function was restored in the 25/35 of those discharged from the intensive care unit. No patient died, and all patients treated with ECMO were successfully weaned.
Conclusion: Children may experience an acute cardiac decompensation due to severe inflammatory state following SARS-CoV-2 infection (multisystem inflammatory syndrome in children - MIS-C). Treatment with immune globulin appears to be associated with recovery of left ventricular systolic function.

Key Words: heart failure; inflammatory cardiomyopathy; SARS-CoV-2; children; COVID-19; atypical Kawasaki disease

Non-standard Abbreviations and Acronyms

MIS-C	Multi-System Inflammatory Syndrome in Children
PICU	Pediatric intensive care unit

Clinical perspective

What is new?

- Multisystem inflammatory syndrome in children (MIS-C) is a new syndrome that is temporally related to previous exposure to the SARS-CoV-2.
- MIS-C shares similarities with atypical Kawasaki disease but prominent clinical signs are largely different.
- Myocardial involvement with acute heart failure is likely due to myocardial stunning or edema rather than to inflammatory myocardial damage.

What are the clinical implications?

- Whereas the initial presentation may be severe with some patients requiring mechanical circulatory and respiratory assistance, rapid recovery with the use of immune globulin and steroids is currently observed.
- Additional study is needed to determine the full spectrum of illness and whether long-term cardiac complications may arise.

Introduction

SARS-CoV-2 infection in children is thought to be relatively mild compared with adult patients, and often asymptomatic or minimally symptomatic (1-3). To date, limited awareness has been afforded to possible SARS-CoV-2-related cardiovascular injury in the pediatric population. However, we recently observed an unexpectedly large number of children hospitalized in intensive care units for cardiogenic shock or acute left ventricular dysfunction in the setting of a multisystem inflammatory state, with a large proportion of those testing positive for SARS-CoV-2.

We describe here a new complex syndrome in 35 children admitted for acute heart failure in febrile patients that is temporally related to previous exposure to SARS-CoV-2 (multisystem inflammatory syndrome in children - MIS-C). We discuss similarities and differences with other pediatric inflammatory diseases with cardiac involvement, as well as current management and preliminary data on early outcomes.

Methods

Study population

The study was approved by the local ethics committee of our institution, which waived the need for patient consent. We will make the data and methods used in the analysis, and materials used to conduct the research available to other researchers for purpose of reproducing the results or replicating the procedures.

We retrospectively collected data for all children with acute left ventricular systolic dysfunction or cardiogenic shock and associated multisystem inflammatory state, admitted to 12 hospitals in France and one hospital in Switzerland from March 22, 2020 to April 30, 2020. All of these institutions are located within the most active COVID-19 pandemic areas in France. The inclusion criteria were the presence of fever (>38.5°C), cardiogenic shock or

acute left ventricular dysfunction (left ventricular ejection fraction <50%) with inflammatory state (C-reactive protein > 100 mg/mL).

Demographic characteristics, clinical data (comorbidities, delay between symptom onset and hospital admission, baseline symptoms and physical signs), laboratory findings (including leukocyte and neutrophil counts, BNP or NT-pro-BNP levels, troponin I levels, IL-6 levels, C-reactive protein, D-dimer), results of cardiac examination (ECG and echocardiography), medical treatments, need for invasive or non-invasive respiratory support, need for mechanical circulatory support, and outcome, were retrieved from patients' files.

COVID-19 diagnosis

All patients were tested for SARS-CoV2 during the hospital course by several means: nasopharyngeal RT-PCR, fecal RT-PCR, tracheal swab, and serology (Chemiluminescent Microplate Immunoassay-CMIA technique). A patient was considered to have a COVID-19 infection if any of these tests were positive.

Statistical analysis

Descriptive statistics were obtained for all study variables. Continuous data were expressed as median and interquartile range [IQR] values. Categorical data were expressed as proportions.

Results

Patient Characteristics

Over a period from March 22nd to April 30th, 2020, 35 patients fulfilling the inclusion criteria with febrile cardiogenic shock or left ventricular dysfunction and inflammatory state were included in the study. Demographic data and clinical features are summarized in Tables 1 and 2. Median age was 10 years. None had underlying cardiac disease. Co-morbidities were limited, and 17% of them were overweight.

SARS-Cov-2 infection

SARS-Cov-2 infection was confirmed in 31/35 patients (88.5%). Nasopharyngeal swab polymerase chain reaction (PCR) was positive in 12 patients (34%), and fecal PCR in 2 patients (6%). Thirty out of thirty-five (86%) patients had positive antibody assays: 23 had IgA and IgG, 3 had IgG, 2 had IgG and IgM, and 2 had IgA only. In addition, two patients were negative for SARS-CoV-2 PCR, but had typical lung CT features of COVID pneumonia. Results are missing in five patients. A history of recent contact with family members displaying viral-like symptoms was reported in 13/35 patients.

Presenting clinical symptoms

All children presented with fever (>38.5°C) and asthenia. Gastrointestinal symptoms were common, with abdominal pain, vomiting or diarrhea present in 80% of patients. Two children underwent emergency operation for suspected appendicitis that was ultimately diagnosed as mesenteric adenolymphitis. Clinical signs suggestive of Kawasaki disease - skin rash, cheilitis, cervical adenopathy, meningism - were frequent, but none of the patients met criteria for a classical form of this disease. Only 6 patients complained of chest pain. The electrocardiogram was not specific, with ST segment elevation in only one patient. The median delay between the first clinical symptoms and symptoms of heart failure was 6 days (IQR, 4.5-6 days). The majority (29/35) were admitted directly to the intensive care unit (ICU). Six patients were initially admitted to the regular pediatric ward but deteriorated within the first 24 hours (median 14 hours after admission in hospital) and were transferred into the ICU.

At admission to the ICU, 80% of patients were in cardiogenic shock requiring the use of intravenous inotropic drugs. Ten/35 patients (28%) required mechanical circulatory assistance with veno-arterial extracorporeal membrane oxygenation (V-A ECMO) that was

successfully weaned and removed in all. Two-thirds had respiratory distress requiring invasive mechanical ventilatory support.

Biology

All patients presented with a severe inflammatory state evidenced by elevated C-reactive protein and D-dimer. Interleukin 6 (n=13) was also elevated (Table 3).

Troponin I elevation was constant but mild to moderate. NT-proBNP or BNP elevation was present in all children.

Cardiac imaging

Echocardiography at admission revealed depressed left ventricular systolic function with an ejection fraction below 30% in 10/35 of patients, and between 30 and 50% in 25/35 patients. The Z-score of left ventricular dimensions was normal at admission in 29/35 patients. Left ventricular hypokinesis was global in 31/35 of patients. Three patients manifested segmental wall hypokinesis. One patient manifested a Takotsubo syndrome presentation with akinesis of the apical segment. Right ventricular function was normal in all patients. Pericardial effusion was present in three cases.

Dilatation of the coronary arteries (Z-score >2 adjusted for body temperature) was found in 6 patients (17%) including five patients with dilatation of the left main stem and one with dilatation the right coronary artery (4). No coronary aneurysm has been observed to date but follow-up has been planned to detect this potential complication.

Treatment

The majority of the patients received intravenous (28/35) inotropic support. First line treatment was intravenous immune globulin in 25/35 of patients. One patient was treated with repeated intravenous immune globulin due to persistent fever 48 hours after first infusion. Twelve patients received intravenous steroids having been considered high-risk patients with symptoms similar to an incomplete form of Kawasaki disease. Finally, three children received

treatment with an interleukin 1 receptor antagonist (anakinra) because of persistent severe inflammatory state. In addition, 23/35 patients were treated with therapeutic dose heparin.

Outcome

Clinical evolution has been favorable thus far for 28/35 patients, with 7/35 either still in the hospital or with residual left ventricular dysfunction (Table 4). At time of submission, all patients but one who was on ECMO had left the hospital after a median hospital stay of 8 days. Complete recovery of left ventricular function was observed in 71% of patients at a median delay of 2 days after admission. Five patients had residual mild to moderate left ventricular systolic dysfunction with a left ventricular ejection fraction >45% at last follow-up (median 12 days). None had a thrombotic or embolic event. Median ICU stay was 7 days (IQR 3.7-10 days) and median hospital stay was 10 days (IQR 8-14 days).

Discussion

We report a cluster of admissions for severe heart failure associated with multisystem inflammatory state in children (MIS-C). These findings contrast with prior reports in children in which the impact of COVID-19 in the pediatric population has been reported to be mild (1). Indeed, among the reported cases of COVID-19, the proportion of patients aged <18 years was 1.7% with relatively few being hospitalized. Further, the number of children admitted to a PICU was 0.6%-2.0% confirming that COVID-19 often has a mild course in children (1,2). A recent alert has been raised by the Pediatric Intensive Care Society in the U.S. and by other groups around the world on the rise in the number of children presenting with this emerging condition (5). It has been observed that they manifested features overlapping with toxic shock syndrome and atypical Kawasaki disease together with cardiac inflammation (MIS-C).

Acute myocardial injury/myocarditis associated with SARS-CoV-2 infection has been described in the adult population from the start of the pandemic (6,7). Further, myocardial

injury has been reported in up to 10-20% of patients infected with SARS-CoV-2 manifesting either as fulminant myocarditis, an ejection fraction decline or myocardial enzyme elevation (8,9). In the present series, the rapid resolution of systolic dysfunction together with mild to moderate troponin elevation suggests that the mechanism of heart failure is not consistent with myocardial damage as seen in adults associated with acute infection with SARS-CoV-2.

Clinical presentation

In the present series, abdominal and gastrointestinal symptoms rather than chest pain were prominent features. All children presented with spiking and remittent fever (>39°C to 40°C) with profound asthenia lasting approximately two days. In a large proportion of patients, the hemodynamic presentation at admission to the PICU was shock with low systemic blood pressure. The association with respiratory distress or reduced consciousness led to rapid initiation of ventilatory support. Pediatric intensivists are accustomed to suspect Kawasaki disease in children presenting with febrile shock particularly in older children and adolescents (10). As some patients manifested signs suggestive of atypical or incomplete Kawasaki disease, these patients were initially managed as severe forms of this disease. Indeed, it is well known that Kawasaki disease signs can be overlooked in this part of the pediatric population. Kawasaki disease shock syndrome manifests mainly with low systolic blood pressure or clinical signs of poor perfusion (11,12). Left ventricular systolic dysfunction is seen only a third of the patients but long-lasting diastolic dysfunction is a prominent finding in this syndrome (11). The syndrome that we present here (MIS-C) may share some aspects of the physiology of Kawasaki shock syndrome, but left ventricular systolic dysfunction was present in all patients in association with low systolic blood pressure. Heart failure was an inclusion criterion in our series but MIS-C can also be observed without overt heart failure (5). Resistance to immune globulin treatment or subsequent development of coronary artery aneurysms may be associated with this new syndrome.

Similarities and differences with Kawasaki disease

Some aspects of this emerging pediatric disease (MIS-C) are similar to those of Kawasaki disease: prolonged fever, multisystem inflammation with skin rash, lymphadenopathy, diarrhea, meningism and high levels of inflammatory biomarkers. But differences are important and raise the question as to whether this syndrome is Kawasaki disease with SARS-CoV-2 as the triggering agent, or represents a different syndrome (MIS-C). Kawasaki disease predominantly affects young children <5 years, whereas the median age in our series is 10 years. Incomplete forms of Kawasaki disease occur in infants who may have fever as the sole clinical finding, whereas older patients are more prone to exhibit the complete form. Left ventricular dysfunction was the main cardiac feature in this series, with a limited number of patients having coronary artery dilatation (Table 2). Myocardial inflammation can be documented in a high proportion of patients with Kawasaki disease and it usually precedes coronary artery abnormalities (13). In Kawasaki disease, myocardial edema is the main finding without ischemic damage and with limited cell necrosis as evidenced by the mild to moderate elevation of troponin I (14). Left ventricular systolic dysfunction improved rapidly in our patients as it does in Kawasaki disease concomitant with a decline in the inflammatory process (15). The high levels of brain natriuretic peptide in our series suggest a mechanism of myocardial edema or stunning. In addition, elevated interleukin-6 levels might also be due to stretched cardiomyocytes and cardiac fibroblasts together with macrophage activation, as these immune cells are the principal producer of interleukin-6 (16). Interleukin-6 levels were very high when measured in our patients, and this might partly explain why some were vasoplegic.

The overlapping features between the condition presented here (MIS-C) and Kawasaki disease may be due to similar pathophysiology. The etiologic agent of Kawasaki disease is unknown but likely to be ubiquitous, causing asymptomatic childhood infection but triggering

the immunologic cascade of Kawasaki disease in genetically susceptible individuals. Please note that infection with a novel RNA virus that enters through the upper respiratory tract has been proposed to be the cause of the disease (17,18).

Relation to SARS-CoV-2

Among the proposed mechanisms for myocardial and lung injury caused by SARS-CoV-2, "cytokine storm" triggered by an imbalanced response by proinflammatory and regulatory T cells has been proposed (19). In our series, almost 90% of patients tested positive for SARS-CoV-2 infection. Besides the low sensitivity of PCR, it is possible that the virus has already been cleared from the upper respiratory tract in our patients, as those who had positive serologic test already had IgG type antibodies (20). This suggests that they had been in contact with the virus more than three weeks before admission. The delay between the pandemic in the general population and the recent emergence of this illness in children is surprising. Yet, this is consistent with the usual sequence of a canonical response to a conventional antigen. There are indeed conflicting data regarding peripheral blood T cell activation during acute Kawasaki disease (21). We successfully used intravenous immune globulin in these patients with adjunctive therapy in some of them. The exact mechanism of action of the immune globulin in Kawasaki disease is unclear, but there is clearly an anti-inflammatory action on monocytes/macrophages and consequently on the amount of circulating inflammatory molecules.

Early diagnosis of this SARS-CoV-2 associated multisystem disease complicated by heart failure (MIS-C) is certainly useful in the present period in identifying children who require treatment and in preventing left ventricular dysfunction and acute heart failure. Since the recent alert in France and other countries, we proposed a simple algorithm in the emergency room for children with prolonged and unexplained fever, including rapid NT-proBNP for urgent specialized evaluation for those with elevated NT-proBNP levels, and

more classical management for those without evidence of early cardiac involvement. Since the start of this protocol three weeks ago, we observed an increase in the number of patients with less severe forms of the disease without heart failure and a stable number of admissions for heart failure with none requiring mechanical assistance.

In our series, the majority of patients received intravenous immune globulin treatment with and without steroids. The use of anakinra was rarely indicated (22). Blocking the cytokine storm that obviously plays a role in this condition might be an alternative treatment in resistant forms that have not been yet encountered in our series. Targeting the interleukin-6 receptor or depleting cytokines by other means represent potential approaches available at this time.

In conclusion, the pediatric and cardiology communities should be acutely aware of this new disease probably related to SARS-CoV-2 infection (MIS-C), that shares similarities with Kawasaki disease but has specificities in its presentation. Early diagnosis and management appear to lead to favorable outcome using classical therapies. Elucidating the immune mechanisms of this disease will afford further insights for treatment and potential global prevention of severe forms. Identifying the genetic bases of individual susceptibility is also key to tailored prevention.

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None.

Disclosures

None.

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Table 1. Clinical signs and symptoms

	Value
Age	
Median	10
Distribution, n	
<1yr	0
1-5 years	1
6-10 years	15
11-16 years	19
Sex, n (%)	
Male	18 (51)
Female	17 (49)
Comorbidity, n (%)	10 (28)
Asthma	3 (8.5)
Lupus	1 (3)
Overweight (BMI > 25)	6 (17)
Signs and symptoms, n (%)	
Asthenia	35 (100)
Fever	35 (100)
Gastrointestinal symptoms	29 (83)
Respiratory distress	23 (65)
Rhinorrhea	15 (43)
Adenopathy	21 (60)
Skin rash	20 (57)
Meningism	11 (31)

Data are median (IQR) or n (%), where n is the total number of patients with available data.

Table 2. Cardiac signs

	n (%)
Clinical signs	
Chest pain	6 (17)
Cardiogenic shock with collapse	28 (80)
Ventricular arrhythmia	1 (3)
Systolic blood pressure at admission (percentile (IQR))	1 (1-10)
Coronary artery dilatation Z-score > +2 Aneurysms at day 10 (echography only)	6 (17) 0 (0)
Left ventricular ejection fraction at baseline, n (%)	
<30%	10 (28)
30-50%	25 (72)
Evolution of LVEF (median±SD)	
Baseline (35 patients)	32±9
Day 3 (23 patients)	52±10
Day 7 (34 patients)	60±6
Recovery left ventricular ejection fraction	
LVEF > 60% at day 7 n (%)	25 (71)
Time to full recovery, days (median and range)	2 (2-5)

Data are median (IQR) or n (%), where n is the total number of patients with available data.

Table 3. Laboratory findings

	Baseline	Peak value (Day) (n patients)	Nadir value (Day) (n patients)	Normal values
High sensitive troponin I (ng/L) (n=35)	347 (186-1267)	408 (258-679) Day 1 (n=16)	28 (18-53) Day 10 (n=16)	<26 ng/ml
Creatinine kinase (U/L) (n=19)	174 (110-510)	-	-	<180 U/L
NT-proBNP (n=5)	41484 (35811 - 52475)	-	-	< 300 pg/mL
BNP (pg/mL) (n=28)	5743 (2648 - 11909)	4256 (2340-6503) Day 1 (n=11)	72 (56-140) Day 7 (n=12)	< 100 pg/mL
D-Dimer (ng/ml) (n=20)	5284 (4069-9095)	-	-	< 500 ng/mL
C-reactive protein, (mg/mL) (n=35)	241 (150-311)	-	-	< 6 mg/mL
Procalcitonin (ng/ml) (n=26)	36 (8-99)	-	-	< 2 ng/mL
White blood cell count, $x10^3$/L (n=35)	16 (12-23)	-	-	< $12x10^3$/L
Neutrophil count, x 10^3/L (n=34)	13 (8-19)	-	-	< $8.5x10^3$/L
Interleukin 6 (pg/mL) (n=13)	135 (87-175)	-	-	< 8.5 pg/mL

BNP Brain natriuretic peptide

Data are median (IQR) or n (%), where n is the total number of patients with available data.

Table 4. Treatment and responses

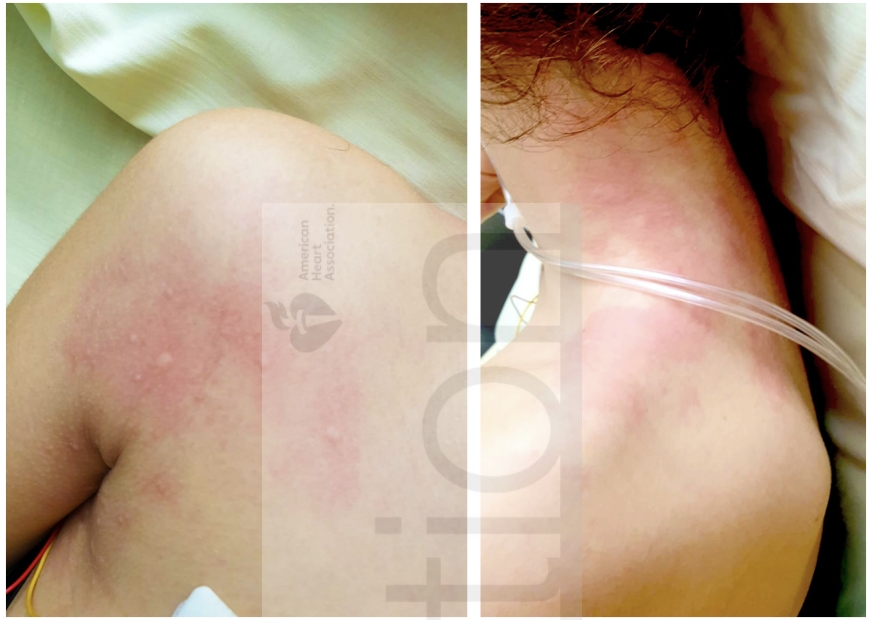
Treatment, n (%)	
Inotropic support	28 (80)
Immunoglobulin infusion	25 (71)
Intravenous corticosteroids	12 (34)
Interleukin 1 receptor antagonist	3 (8)
Anticoagulation with heparin	23 (65)
Respiratory support, n (%)	33 (94)
Invasive	22 (62)
Non invasive	11 (32)
VA-ECMO, n (%)	10 (28)
ECMO duration in days (range)	4.5 (3-6)
Recovery left ventricular ejection fraction	
LVEF > 60% at day 7 n (%)	25 (71)
Death, n (%)	0 (0)

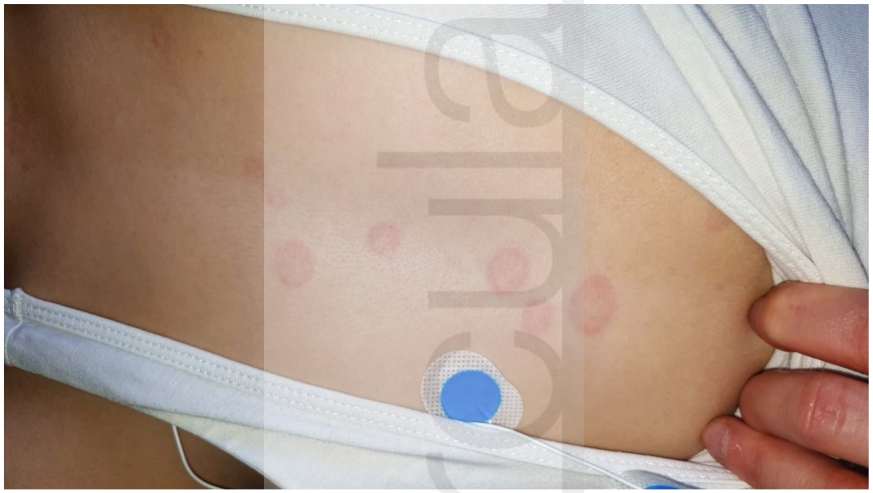
VA ECMO: veno-arterial Extracorporeal membrane oxygenation.
Data are median (IQR) or n (%), where n is the total number of patients with available data.

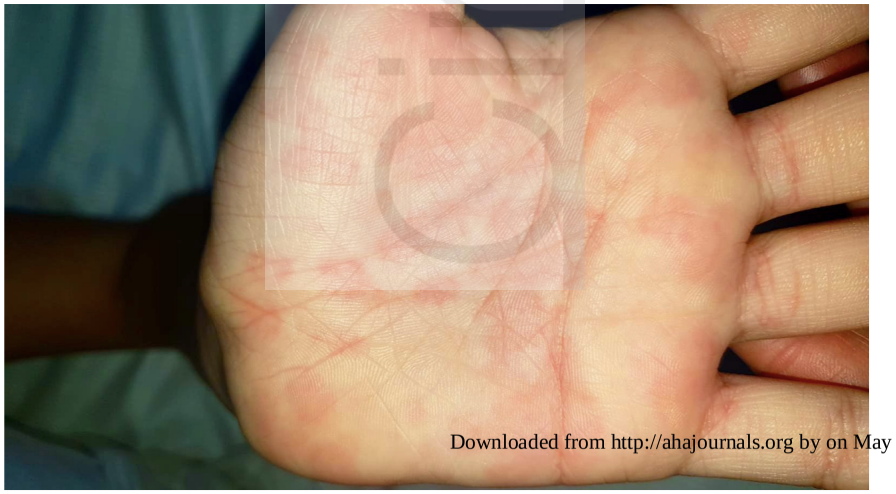
Figure Legends

Figure 1: Maculo-papular rash in a 12-year old girl.

Figure 2: Schematic representation of the clinical signs in severe forms of SARS-CoV-2 related multisystem inflammation. Red text indicates signs or symptoms consistent with Kawasaki disease. In black, signs that are rare in Kawasaki disease. Percentages are those present in the present series of patients.







SARS-COV-2 related multisystem inflammation

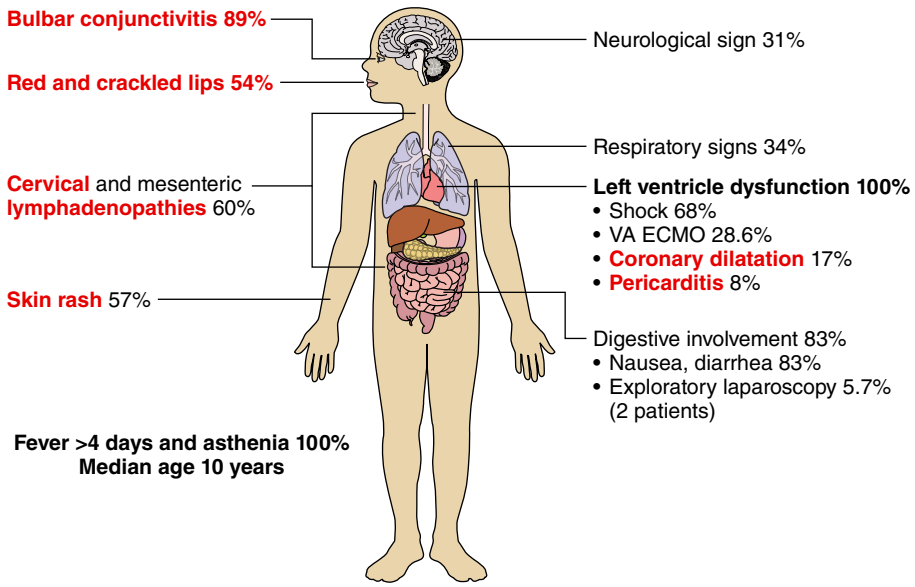


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Figure: 01